

Investigation of Critical Parameters of an Emulsion-Solvent Extraction Based Microsphere Preparation Process

Harri Heiskanen

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Harri Heiskanen

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Abstract

The aim of this PhD thesis was to develop further the novel hydrocarbon-in-fluorocarbon emulsion solvent extraction based microsphere preparation process. In the first step of the process an emulsion was produced. The dispersed phase of the emulsion contained the matrix material of the microspheres. In the second step of the process, the hydrocarbon from the dispersed phase was extracted into the continuous phase by mixing the emulsion with the excess of the perfluorocarbon. Two different solidification strategies were used: I) the emulsion formed in a vessel was transferred into another vessel containing an excess of the perfluorocarbon, and II) the excess of the perfluorocarbon was added to the emulsion. The critical emulsification and solidification parameters affecting the size, the size distribution, and the morphology of the microspheres were investigated.

A good agreement between the size of the microspheres and the Weber number (emulsification step) was found. With the preparation method I, the mixing conditions in the solidification step also affected the size of the microspheres, partly because the stability of the hydrocarbon-in-perfluorocarbon emulsion was poor.

The size of the microspheres was affected not only by the surfactant concentration but also by the volume ratio of the dispersed phase to the continuous phase. At a low volume ratio of the phases, the surfactant concentration was the dominating factor, whereas the volume ratio of the phases was the dominating factor at a high volume ratio.

The viscosity of the phases affected the size of the microspheres. The viscosity of the dispersed phase decreased with a decreasing matrix material concentration and as a result, the size of the microspheres decreased. The size of the microspheres decreased as the continuous phase viscosity increased.

The morphology of the microspheres could be controlled by changing the solidification rate. The solidification rate was adjusted by changing the temperature of the perfluorocarbon used in the solidification step and the hydrocarbon concentration of the perfluorocarbon used in the solidification step. The compactness of the microspheres increased with a decreasing solidification rate.

Keywords Microsphere, Solvent Extraction, Emulsion

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Emulsio – liuotin uutto menetelmään perustuvan mikropartikkelien valmistusprosessin kriittisten parametrien tutkimus

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Väitöskirjassa tutkittiin emulsio – liuotin uutto menetelmään perustuvaa mikropartikkelien valmistusprosessia. Prosessin ensimmäisessä vaiheessa muodostetaan hiilivety-perfluorihiihivety emulsio, jossa valmistettavien mikropartikkelien matriisiaines on liuenneena emulsion dispergoituun faasiin (hiilivety). Toisessa vaiheessa emulsion dispergoitua faasissa oleva hiilivety uutetaan emulsion jatkuvaan faasiin (perfluorihiihivety) sekoittamalla emulsio ylimäärään perfluorihiihivetyä. Tällöin muodostuu kiinteitä mikropartikkeleita ja vain yksi nestefaasi. Mikropartikkelien kiinteytyksessä käytettiin kahta eri strategiaa: I) emulsio siirrettiin toiseen sekoitusreaktoriin, jossa oli ylimäärin perfluorihiihivetyä, ja II) ylimäärä perfluorihiihivetyä lisättiin emulsioon. Väitöskirjatyössä tutkittiin valmistusolosuhteiden vaikutusta mikropartikkelien kokoon, kokojakaumaan ja morfologiaan.

Mikropartikkelien koon ja Weberin luvun välillä havaittiin selvä korrelaatio. Kiinteytysvaiheen sekoitusolosuhteet vaikuttivat myös mikropartikkelien kokoon valmistusmenetelmässä I, koska käytetyn hiilivety-perfluorihiihivety emulsion stabiilisuus on heikko.

Valmistettujen mikropartikkelien koko ei riippunut pelkästään pinta-aktiivisen aineen määrästä, vaan myös dispergoitun ja jatkuvan faasin tilavuussuhteesta. Pinta-aktiivisen aineen määrä oli määräävä tekijä alhaisissa faasien tilavuussuhteissa, kun taas tilavuussuhde oli määräävä tekijä korkeissa tilavuussuhteissa.

Emulsion faasien viskositeetti vaikutti mikropartikkelien kokoon. Dispergoitun faasin viskositeetti laski matriisiaineksen pitoisuuden pienentyessä ja tämän seurauksena mikropartikkelien koko pieneni. Mikropartikkelien koko pieneni jatkuvan faasin viskositeetin kasvaessa.

Mikropartikkelien morfologiaa muokattiin muuttamalla mikropartikkelien kiinteytymisnopeutta. Kiinteytymisnopeutta vaihdeltiin muuttamalla kiinteytykseen käytettävän perfluorihiihivedyn hiilivety-pitoisuutta ja lämpötilaa. Valmistetut mikropartikkelit olivat tiiviimpiä kiinteytymisnopeuden hidastuessa.

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PREFACE

The experimental work for this thesis was carried out at the laboratories (Innovation center and BC*-pilot) of Borealis Polymers Oy during the years 2007-2009. The study was financially supported by Borealis Polymers Oy.

I especially thank my supervisor Dr. Peter Denifl. I admire his knowledge and experience in catalyst synthesis. This thesis was done under supervision of two professors. I thank Professor Markku Hurme (2007-2012) for valued support and advice, and also Professor Jukka Koskinen (2012) for his support during the final stages of my thesis. I want to also thank co-author Dr. Päivi Pitkänen and Dr. Holger Pöhler who offered this PhD-work for me.

In addition to my supervisor and co-authors, I thank Jenni Valonen for the discussions related to the experimental work. I thank Dr. David Quin for revising the language of the publications I-V. I owe my deepest thanks to the BC*-Pilot personnel for providing relaxed and enjoyable working atmosphere. Thanks go to all co-workers at Borealis Polymers Innovation center, and especially I want to thank Soile Rautio and Tiina Vanne for pleasant working atmosphere. I want to thank Vuokko Ojanperä for performing the scanning electron microscopy and Leila Kettunen for measuring the particle size distributions.

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Espoo, October 7th 2012

Harri Heiskanen

LIST OF PUBLICATIONS

This thesis is based on the following five publications, hereinafter referred to in the text by their Roman numerals I-V.

I Heiskanen, H., Denifl, P., Hurme, M., Pitkänen, P., Novel preparation and properties of microspheres involving a hydrocarbon-perfluorocarbon solvent extraction process, *Chemical Engineering & Technology* **33** (2010) 682-691.

II Heiskanen, H., Denifl, P., Hurme, M., Pitkänen, P., Effect of emulsification conditions on the properties of the microspheres prepared using a solvent extraction process, *Chemical Engineering & Technology* **33** (2010) 1635-1644.

III Heiskanen, H., Denifl, P., Hurme, M., Pitkänen, P., Oksman, M., Effect of physical properties and emulsification conditions on the microsphere size prepared using a solvent extraction process, *Journal of Dispersion Science and Technology* **33** (2012) 234-244.

IV Heiskanen, H., Denifl, P., Pitkänen, P., Hurme, M., Effect of preparation conditions on the properties of the microspheres prepared using an emulsion-solvent extraction process, *Chemical Engineering Research and Design* **90** (2012) 1517-1526.

V Heiskanen, H., Denifl, P., Pitkänen, P., Hurme, M., Effect of concentration and temperature on the properties of the microspheres prepared using an emulsion-solvent extraction process, *Advanced Powder Technology*, doi:10.1016/j.apr.2011.10.007.

AUTHOR'S CONTRIBUTION

Publications I-V: The author designed and carried out the experiments. The results were interpreted and the manuscripts were written together with the co-authors.

ABBREVIATIONS

MAO methylaluminoxane

PFC hexadecafluoro-1,3-dimethylcyclohexane

Symbols

a coefficient

A coefficient

b coefficient

c coefficient

c_i coefficient i

d coefficient

d_i diameter of particle i , m

d_{max} maximum stable droplet size, m

d_p diameter of particle, m

d_{32} Sauter mean diameter, m

D diameter of stirrer, m

D_i diffusivity, m^2/s

D_p diameter of droplet, m

D_v diffusivity inside droplet, m^2/s

k_c mass transfer coefficient on the interface of a droplet/particle, m/s

k_{ci} internal mass transfer coefficient of a droplet/particle, m/s

k_i coefficient i

n_i number of droplets/particles in the i th interval ($d_i - d_{i-1}$),

dimensionless

N stirring speed, 1/s

R_o radius of initial droplet, m

R_c radius of core, m

Re Reynolds number, dimensionless

Sc Schmidt number, dimensionless

Sh Sherwood number, $Sh = (k_c \cdot d_p) / D_i = 2 + 0.6 Re^{1/2} Sc^{1/3}$,

dimensionless

u velocity of flow, m/s

$u_{e,c}$ combined emulsion velocity, m/s

$u_{e,f}$ emulsion addition velocity, m/s

u_{ts} stirrer tip speed, m/s

Vi viscosity group, dimensionless

We Weber number, $= (\rho_c N^2 D^3) / \sigma$, dimensionless

Greek letters

μ_c viscosity of continuous phase, Pa s

μ_d	viscosity of dispersed phase, Pa s
ρ_c	density of continuous phase, kg/m ³
ρ_d	density of dispersed phase, kg/m ³
ρ_l	density of melted phase, kg/m ³
ρ_s	density of solid phase, kg/m ³
σ	interfacial tension, N/m
Φ_d	volume fraction of disperse phase, dimensionless

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1. INTRODUCTION

Emulsification-solvent extraction/evaporation processes are widely used to produce microspheres, mainly for the controlled release of drugs, cosmetics, inks, pigments, and chemical reagents. Microsphere preparation by an emulsion-based solvent extraction method consists of four major steps as shown in Figure 1: 1) the matrix material is first dissolved in the solvent; this solution will form the dispersed phase of the emulsion, 2) the emulsion is formed by mixing the dispersed phase and the continuous phase for example in a stirred vessel, 3) after the desired droplet size distribution is achieved the solvent is extracted from the dispersed phase into the continuous phase by mixing the emulsion with an excess continuous phase, forming solid microspheres, and 4) the microspheres are separated and dried. In solvent extraction, the volume and composition of the continuous phase is chosen such that the entire volume of the dispersed phase solvent can be extracted. In the solvent evaporation process, the capacity of the continuous phase is insufficient to dissolve the entire volume of the dispersed phase solvent. Therefore, the solvent must be evaporated from the surface of the emulsion to yield solid microspheres.

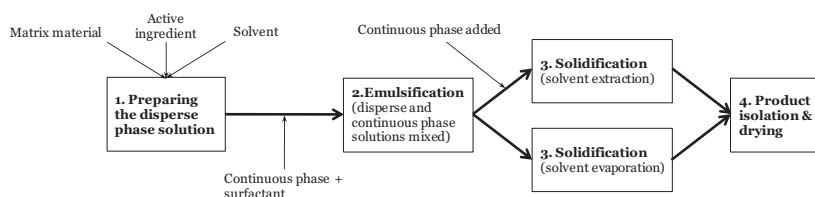


Figure 1. Schematic diagram of a microsphere preparation process using either a solvent extraction or evaporation process.

Understanding the parameters affecting the size, the size distribution and the morphology of the microspheres is essential, for example in order to have controlled and repeatable drug release from the microspheres. The relationship between the size of the microspheres produced and the process parameters is complicated. In principle, the size of the microspheres produced is influenced by all the process parameters associated with liquid-liquid emulsification. Additionally, the solidification conditions affect greatly the size and the morphology of the microspheres. Freitas et al.

(2005) and Li et al. (2008) have written recent reviews about emulsion based microsphere preparation processes.

The aim of this PhD thesis was to develop further a novel hydrocarbon-in-fluorocarbon emulsion based microsphere preparation concept (Denifl et al., 2003) and to determine the critical emulsification and solidification parameters affecting the size, the size distribution, and the morphology of the microspheres. The results obtained were compared to the results achieved with commonly used emulsion systems (oil-in-water or water-in-oil) to see if any similar physical phenomena dominate during microsphere preparation using the hydrocarbon-fluorocarbon emulsion.

2. STATE OF THE ART

Emulsification and solidification are the critical steps of the emulsion based microsphere preparation process. In the emulsification step, the size and size distribution of the microspheres are pre-determined while in the solidification step, it is mainly the morphology of the microspheres that is determined.

2.1 Emulsification

Emulsions of two immiscible liquids are usually produced by applying mechanical energy. Viscous forces exerted by the continuous phase can also produce droplets. There are lots of different systems to produce emulsions: stirred vessel, rotor-stator (Atiemo-Obeng and Calabrese, 2004), membrane (Charcosset et al., 2004; Gijsberten-Abrahamse et al., 2004; Vladisavljevic and Williams, 2005), and static mixer (Thakur et al., 2003). High-pressure systems (Schultz et al., 2004), capillary systems (Christopher and Anna, 2007), microfluidics (Luo et al., 2011), and ultrasonic systems (Canselier et al., 2003) are also used in emulsification. In the following chapters the main focus is on emulsification using the stirred vessel technique.

2.1.1 Formation of emulsion

Emulsion is a state in which the continuous break-up and coalescence of droplets occur. The final droplet size is the result of the droplets break-up, which decreases the mean droplet size, and coalescence of the droplets, which increases the mean droplet size. Upon droplet breakage, the surfactant (if present) adsorbs onto the newly formed interfaces, preventing the droplets from coalescence. A variety of system variables ranging from the physical properties of the liquids, volume ratio of the dispersed phase to

the continuous phase, surfactant concentration, mixing intensity, temperature and type of mixer, all have an effect on the mean emulsion droplet size and the droplet size distribution of the emulsion.

Droplet break-up

In a stirred vessel the droplets are continuously broken up by the mechanical forces induced by the surrounding fluid. The forces causing droplet break-up are extremely non-uniform. Velocity gradients are highest near the impeller and diminish rapidly with the distance from the impeller.

All the dynamical fluid forces that cause droplet deformation are commonly referred to as shear forces. The restoring forces are surface and internal viscous forces; these tend to maintain the size and the shape of the droplets. Droplet break-up occurs when the shear forces exceed the restoring forces. As the diameter of the droplet decreases, the shear forces across it also decrease, and conversely the restoring forces increase. An equilibrium droplet size is finally achieved once the shear forces are unable to break up the droplet.

The theory of Kolmogorov and Hinze assumes that droplets existing in the inertial region of turbulence have a maximum droplet size, d_{\max} . The maximum stable droplet size in dilute dispersions under fully turbulent conditions can be estimated from the balance between the shear forces tending to break up the droplet and the resistance forces holding the droplet together using the Weber number, We :

$$\frac{d_{\max}}{D} = c \left(\frac{\rho_c N^2 D^3}{\sigma} \right)^{-0.6} = c We^{-0.6} \quad (1)$$

The maximum droplet diameter correlates linearly with the Sauter mean diameter, d_{32} (Sprow, 1967). Therefore the above Equation (1) can be written:

$$\frac{d_{32}}{D} = c_2 We^{-0.6} \quad (2)$$

However, some experimental results do not support that $d_{32} = A d_{\max}$ nor that the exponent on the Weber number is -0.6 (Equation 2) (Mu et al., 2005; Pacek et al., 1998; and Zhou and Kresta, 1998).

The Sauter mean diameter is used extensively in the characterization of liquid-liquid and gas-liquid dispersions. It links the area of the dispersed phase to its volume and hence to mass transfer and chemical reaction rates. It is calculated by the following Equation:

$$d_{32} = \frac{\sum n_i d_i^3}{\sum n_i d_i^2} \quad (3)$$

Droplet coalescence

Coalescence involves the interaction of the continuous phase flow and two droplets. Coalescence can be divided into three sequential steps: the approach of two droplets, film drainage between the droplets, and rupture. Once the collision occurs, the continuous phase between the droplets is squeezed into a film. The film drains as the droplets continue approaching by the bulk flow field. The film drainage rate can be determined by the rigidity and the mobility of the interface (Chesters, 1991). The rigidity of the interface is a function of the interfacial tension and determines how much the droplet flattens during film drainage. The mobility of the interface depends on the viscosity ratio of the phases and determines the type of flow occurring during film drainage. Coalescence will occur if the interaction time exceeds the time required for drainage to the critical film thickness. Coalescence is greatly favored by low dispersed phase viscosity, high dispersed phase content, and high power input.

Emulsions are thermodynamically unstable, as droplets tend toward coalescence. Coalescence immediately after droplet break-up can be reduced or even totally avoided by using a surfactant and/or by affecting the hydrodynamic effects using a stabilizer (Tesch and Schubert, 2002). The surfactant is a surface-active compound. As the droplet breaks up, a new liquid-liquid interface is created. Coalescence is prevented if the surfactants are absorbed into the new liquid-liquid interface quickly enough. The surfactant reduces interfacial tension between the phases. The decreased interfacial tension reduces coalescence because it leads to greater flattening of the droplets during collision. Therefore, more continuous phase is trapped between the droplets. The drainage time increases and as a result, the likelihood of coalescence decreases. The stabilizer is not surface-active like a surfactant. A stabilizer increases the continuous phase viscosity, therefore, the mobility of the droplets and their collision frequency are decreased. At a higher continuous phase viscosity the drainage time increases, while the collision time remains the same, resulting in reduced coalescence.

2.1.2 Effect of emulsification conditions on microsphere properties

The mean droplet size and the droplet size distribution of the emulsion depend on the conditions of the mixing as well as on the physical properties of the two liquids. The mean size of the emulsion droplets is larger than the mean size of the microspheres because the solvent is extracted from the solidifying droplets. The size of the microspheres can be also affected by the

mixing conditions of the solidification step if those differ significantly from the mixing conditions of the emulsification step.

Stirring speed

The effect of the stirring speed on microsphere size has been widely studied. In general, an increase in tip speed increases the Weber number (Equation 1), therefore, higher shear forces are created and smaller microspheres are produced (Gabor et al., 1999; Jégat and Taverdet, 2000; Mateovic et al., 2002; Nepal et al., 2007).

A high stirring speed has been reported to result in the formation of microspheres with narrow microsphere size distribution (Gabor et al. 1999). Increasing the stirring speed increases the Reynolds number. The microsphere size distribution becomes narrower and the number of large droplets is drastically reduced as the Reynolds number increases (Mu et al., 2005).

Correlations between the Sauter mean diameter of microspheres and the Weber number have been presented (Bahukudumbi et al., 2004; Mu et al., 2005): the size of the microspheres decreases as the Weber number increased. The presented exponents for Equation (2) were -0.53 (Bahukudumbi et al., 2004) and -0.72 (Mu et al., 2005). Both values were close to the theoretical value of -0.6. In the latter case, the deviation from the theoretical exponent value was attributed to the fact that the flow was not turbulent during the microsphere preparation.

Surfactant

A surfactant contains usually a hydrophobic head group and a hydrophilic tail group. Therefore, the surfactant contains both a water insoluble and a water soluble part. In the case of fluorosurfactants commonly the tail group is fluorocarbon compound. Surfactants can be classified according to the head group. A non-ionic surfactant has no charge groups in its head group. An anionic surfactant contains a positively charged head group whereas a cationic surfactant contains a negatively charged head group. A surfactant is zwitterionic if the head contains two oppositely charged groups.

The addition of a surfactant is known to reduce interfacial tension, coalescence of the droplets and mass transfer through the interface of the phases. Therefore, the surfactant affects both the emulsification and the solidification of the microsphere preparation process.

A surfactant is known to decrease the interfacial tension between the phases. The interfacial tension decreases with the increasing bulk concentration of the surfactant, until the critical micelle concentration is reached. A further increase in the bulk concentration of the surfactant does not alter the interfacial tension. The decreased interfacial tension reduces

the size of the emulsion droplets (Equation 1) and the coalescence of droplets, as explained in the Chapter 2.1.1. At low surfactant concentrations, the dynamic and static interfacial tensions may differ. This interfacial tension gradient may affect the droplet break-up by increasing the turbulent stress and hence result in a decrease in the droplet size (Koshy et al., 1988). At zero and high surfactant concentrations, there is no difference between the dynamic and the equilibrium interfacial tension.

The effect of the surfactant type and concentration on the size of the emulsion droplets has been studied (Tcholakova et al., 2004). It was shown that there were two regimes: I) a surfactant-poor regime, in which the droplet size was strongly dependent on the surfactant concentration; II) a surfactant-rich regime, in which the size of the emulsion droplets did not depend on the surfactant concentration but was determined by the interfacial tension and the power dissipation density.

A surfactant reduces the mass transfer coefficient on the interface of a droplet and hence affects the solidification process of microspheres. Two models are widely accepted to explain reduced mass transfer through the interface of the phases due to the surfactant. The surfactant on the interface forms an interfacial barrier layer, called a physicochemical effect. The second model is based on hydrodynamic behavior: the surfactant modifies the hydrodynamic behavior of the moving droplet in a number of ways and therefore the mass transfer through the interface is reduced. Studies have shown that the mass transfer coefficient will decrease rapidly with increasing surfactant concentration. The mass transfer coefficient either approaches a constant value, or decreases to a minimum value and then increases slightly with further addition of surfactant.

Chen and Lee (2000) studied the effect of surfactants on mass transfer in liquid-liquid extraction. All the surfactants tested reduced the mass transfer rate significantly. The effectiveness of reducing the mass transfer had no direct relation to the ionic type of the surfactants, but it was affected by the adsorption rate and the adsorbed surface concentration on the interface. The additional mass transfer resistance in the presence of the surfactants was found to result mainly from the obstruction of the adsorbed surfactant layer, and was related to the surfactant concentration. Lee (2003) studied the effect of the surfactants on the mass transfer during the droplet formation and the droplet falling stage. The surfactants that most effectively decreased the interfacial tension always exhibited the highest effectiveness in mass transfer inhibition. The mass transfer inhibition of the surfactant was mainly caused by the hydrodynamic effect in the droplet formation stage and from the obstruction of the barrier layer in the droplet falling stage.

As a result of the addition of a surfactant, the interfacial tension between the phases decreases and coalescence is reduced, hence the mean size of the droplets decreases in the emulsification step. Therefore, the size of the microspheres decreases at the same mixing speed as the surfactant concentration is increased. The mean size of the microspheres has been reported to decrease almost linearly with increasing surfactant concentration (Mu et al., 2005; Rafati et al., 1997). Nepal et al. (2007) also noticed an almost linear decrease in the mean size of the microspheres as the surfactant concentration increased from 0.2 to 0.8 % (w/v). However, the mean size of the microspheres remained constant as the surfactant concentration was further increased to 1.2 % (w/v).

The surfactant concentration has been reported to affect the morphology of microspheres and the drug distribution within the microspheres (Yang et al., 2001). A low surfactant concentration increased the size of the pores in the inner structure of the microspheres. The drug distribution within microspheres fabricated at a high surfactant concentration was more uniform than at low surfactant concentrations.

Temperature

The microsphere preparation temperature has been shown to affect microsphere properties significantly. A higher temperature reduces the viscosity of the emulsion phase, and lowers the interfacial tension, thereby reducing the energy needed to create smaller droplets (Equation 1). Therefore, smaller microspheres should be produced at higher temperatures with the same stirring speed. However, opposite results have been presented: the mean size of the microspheres increased as the preparation temperature increased (Mateovic-Rojnik et al., 2005; Yang et al., 2000a) when the microspheres were produced using a solvent evaporation method. With a solvent extraction method (Yang et al., 2000b), an increase in the preparation temperature from 4 to 29 °C led to a decrease in the microsphere size. At higher preparation temperature, the viscosity of the dispersed phase was lower and therefore the droplets broke up more easily, resulting in the decrease in the size of the microspheres. However, at high preparation temperatures (above 29 °C) larger microspheres were produced, probably due to the rapid solvent evaporation.

The microsphere size distribution has been shown to broaden with an increasing preparation temperature (Mateovic-Rojnik et al., 2005; Yang et al., 2000a). Mateovic-Rojnik et al. (2005) explained the broader size distribution in that, at higher preparation temperatures, the solidification process was faster than at lower preparation temperatures. Hence, the droplets were not affected by the shear forces as long as at low preparation temperatures. In the author's opinion, another reason for the increased

microsphere size and broader size distribution could be the increased coalescence of droplets at higher temperatures. As the preparation temperature increases, the continuous phase viscosity decreases resulting in an increased film drainage rate during the coalescence of the droplets. Hence, the coalescence might increase and could result in an increase in the size of the microspheres as well as widening the microsphere size distribution.

Mateovic-Rojnik et al. (2005) reported the effect of preparation temperature on microsphere morphology. At a low preparation temperature, microspheres with irregular shape were produced but the sphericity of the microspheres improved gradually with a rising preparation temperature. The solidification process at low preparation temperatures was slow and therefore the viscosity of solidifying droplets increased slowly. The shear forces deformed the solidifying droplets continuously. The shape of the solidifying droplets no longer returned to a thermodynamically more favorable spherical shape because the viscosity of the solution was high. Therefore, irregular-shaped microspheres were produced at a low preparation temperature. The microsphere surface roughness decreased with an increasing preparation temperature.

Viscosity

It is common to vary the viscosity of the dispersed phase, but the viscosity of the continuous phase is rarely varied in the microsphere preparation processes. The increased viscosity of the dispersed phase increases the size of the microspheres at the same mixing speed because higher shear forces are necessary to break up the more viscous droplets. By increasing the continuous phase viscosity, the film drainage rate decreases, therefore, the droplet coalescence is reduced, and the size of the microspheres decreases. However, a raised continuous phase viscosity can complicate the recovery of the microspheres. The apparent emulsion viscosity is significantly higher than the pure component viscosities, this is due to both the large quantities of adsorbed surface-active materials and to the large interfacial areas, causing internal flow resistance (Leng and Calabrese, 2004).

Calderbank (1958) presented an empirical equation that describes the impact of viscosity on the Sauter mean diameter:

$$d_{32} = a \left(\frac{\mu_d}{\mu_c} \right)^{0.25} \quad (4)$$

a in the above equation depends on the Weber number and the volume ratio of the dispersed phase to the continuous phase. In other studies, the droplet size has been proportional to $\mu_d^{0.004-0.4}$ and $(1/\mu_c)^{0.02-0.56}$ depending on the system used (Maa et al., 1996a-c; Urban et al., 2006). Wang and

Calabrese (1986) presented a correlation between the Sauter mean diameter and the Weber number, taking into account the viscosity of the dispersed phase:

$$\frac{d_{32}}{D} = 0.053We^{-0.6}(1 + 0.97Vi^{0.79})^{0.6} \quad (5)$$

where the viscosity group, Vi , represents the ratio of the dispersed phase viscosity to the surface forces:

$$Vi = \frac{\mu_d ND}{\sigma} \left(\frac{\rho_c}{\rho_d} \right)^{0.5} \quad (6)$$

The matrix concentration of the dispersed phase has been shown to have an effect on the size and the morphology of the microspheres. An increase in the matrix concentration increases the viscosity of the dispersed phase. Therefore, a high matrix concentration yields larger microspheres at the same stirring speed (Yang et al., 2000b; Yang et al., 2001; Badri Viswanathan et al., 1999; Rafati et al., 1997; Nepal et al., 2007; Gabor et al., 1999; Mao et al., 2008; Choi et al., 2002; D'Aurizio et al., 2011) because higher shear forces are necessary to break up the more viscous droplets.

A low dispersed phase matrix concentration has been shown to result in the production of microspheres with a narrow size distribution (Gabor et al., 1999; D'Aurizio et al., 2011). A similar phenomenon was also noticed in emulsion droplet size distribution, which became narrower with decreasing droplet viscosity (Wang and Calabrese, 1986). The matrix concentration has also been shown to affect the morphology of the microspheres (D'Aurizio et al., 2011).

Volume ratio

Ideally, a dilute system is one in which dispersion is only affected by hydrodynamics. The volume ratio of the dispersed phase to the continuous phase is considered to be < 0.01 in a dilute system. In such a system, each droplet is a single entity experiencing continuous phase fluid forces. Coalescence of droplets can be neglected because few collisions occur. For systems with a volume ratio of the phases > 0.05 , coalescence of droplets can be considered significant depending on the system. Emulsions with a volume ratio of the phases < 0.2 are considered to be moderately concentrated systems. The ideal dilute dispersion theory may still apply to a moderately concentrated system unless it is a coalescing system. The mean size of the emulsion droplets can be predicted for moderately concentrated systems even if some coalescence of droplets occurs. The coalescence of the droplets can be reduced by the addition of a surfactant or by using a stabilizer (see Chapter 2.1.1). The rate of the coalescence increases with an increasing volume of the dispersed phase due to both the increased collision

frequency and to the rheological changes that enable longer contact intervals to be obtained (Leng and Calabrese, 2004).

Modified correlations between the Sauter mean diameter and the Weber number have been presented, which take into account the volume ratio of the phases (Godfrey et al., 1989; Davies, 1992; Shinnar and Church, 1960; Shinnar 1961; Calderbank 1958). The correlation presented by Godfrey et al. (1989) and Davies (1992) is expressed as follows:

$$\frac{d_{32}}{D} = k_1(1 + k_2\Phi_d)We^{-0.6} \quad (7)$$

The term $(1 + k_2\Phi_d)$ in the above Equation (7) reflects the influence of the dispersed phase in reducing the overall level of turbulence in the system. Turbulent damping is thought to be the main reason for the increased droplet size at a large volume ratio of the phases. An increase in the volume ratio of the phases results in a growing droplet collision rate, which leads to an increasing number of break-ups and coalescence of droplets. A break-up is in principle the result of the collision between a droplet and an eddy. Coalescence is the result of the collision of two droplets with each other. Therefore, the number of collisions between two droplets increases stronger with an increased volume ratio of the phases than the break-up collisions between droplets and eddies. Therefore, the mean size of the droplets can increase as the volume ratio of the phases is increased.

The empirical equations (for example, Equation 7) predict that the increased volume ratio of the phases increases the mean droplet size of the emulsion, therefore, resulting in the formation of larger microspheres. However, such a clear correlation between the volume ratio of the phases and the size of microspheres has not been confirmed. Gabor et al. (1999) reported that the mean size of the microspheres decreased as the volume ratio of the phases was increased. A further increase in the volume ratio of the phases increased the mean size of the microspheres. Jeffery et al. (1993) reported that the size of the microspheres increased as the volume of the external aqueous phase was increased. The increase in the size of the microspheres was attributed to a reduction in the agitation because of the decrease in mixing efficiency associated with larger volumes. Ellis and Jacquier (2009) reported that the size of the microspheres increased when the volume ratio of the phases was increased. A further increase in the volume ratio of the phases to 20 (v/v)-% did not have a significant effect on the size of the microspheres. It was assumed that the emulsion became more viscous when the dispersed phase volume was increased. Hence, the size of the microspheres increased.

2.2 Solidification of microspheres

The solidification process is a coupled heat and mass transport system. The following physical phenomena occur during the solidification step: the extraction of the solvent from the droplet, the shrinkage of the solidifying droplet, the change in the temperature and the diffusion of the solvent inside the solidifying droplet. Finally, all the solvent is extracted from the solidifying droplet and a solid microsphere is formed. The solidification rate determines the morphology of the microspheres.

Solidification can be done using either a solvent extraction or a solvent evaporation method (Figure 1). In both solvent extraction and evaporation methods, the solvent of the dispersed phase must be partly miscible in the continuous phase. In the solvent extraction method, the volume and the composition of the continuous phase is chosen so that the entire volume of the dispersed phase solvent can be extracted into the continuous phase. In solvent evaporation, the capacity of the continuous phase is insufficient to extract the entire volume of the dispersed phase solvent. Therefore, the solvent must be evaporated from the surface of the emulsion to yield solid microspheres.

The solvent extraction from the droplet increases the matrix concentration of the solidifying droplet. When a critical matrix concentration is reached, a phase transition (gelation) will take place, beginning on the droplet surface. The solidifying droplets will continue to decrease in size due to the loss of solvent and the reorganization of the matrix molecules during the solidification, unless a rigid crust is formed. The crust decreases the solvent mass transfer rate. If the solvent diffusion from the droplet through the interface into the continuous phase is not too fast compared to the diffusion of solvent inside the droplet, a low concentration gradient of the matrix material is formed inside the solidifying droplet. Therefore, a rigid crust is not formed and the solidifying droplet can shrink during the solidification. As a result, in a slow solidification process dense microspheres are formed (Figure 2).

Fast extraction of the solvent from the dispersed phase into the continuous phase creates a high supersaturation of the matrix material at the surface of the solidifying droplets. If this coincides with the slow diffusion of the solvent inside the solidifying droplet, a high matrix concentration gradient is formed inside the solidifying droplet. The high supersaturation formed results in the precipitation of the matrix material onto the surface of the solidifying droplet and a solid crust is created. If the crust is permeable to the solvent, the diffusion of the solvent will form a hollow core in the microsphere (Figure 2). Klima and Kotalík (1997)

assumed that the crust formation is sufficiently fast and that the final particle size is the same as the initial melted particle size. A simple estimate for the radius of the hollow core (melted particle is cooled and solidified) was given:

$$R_c = R_0 \left(1 - \frac{\rho_l}{\rho_s} \right)^{1/3} \quad (8)$$

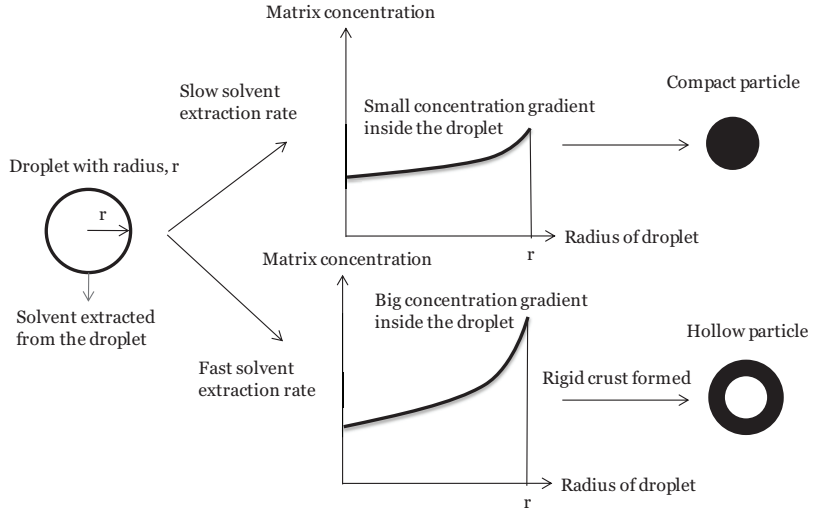


Figure 2. Solidification of a droplet resulting in the formation of either a compact/dense microsphere or a hollow microsphere.

The mass transfer coefficient, k_c , on the interface of a droplet/particle can be estimated using the Sherwood (Sh), Reynolds (Re), and Schmidt (Sc) numbers (McCabe et al., 1993):

$$Sh = \frac{k_c d_p}{D_i} = 2 + 0.6 Re^{1/2} Sc^{1/3} \quad (9)$$

$$Re = \frac{\rho_c d_p u}{\mu_c} \quad (10)$$

$$Sc = \frac{\mu_c}{\rho_c D_i} \quad (11)$$

The relationship in Equation (9) is known as the Frössling correlation. If $Re > 25$ then Equation (9) becomes (McCabe et al., 1993):

$$Sh = \frac{k_c d_p}{D_i} = 0.6 Re^{1/2} Sc^{1/3} \quad (12)$$

$$\rightarrow k_c = 0.6 \frac{D_i^{2/3}}{(\mu_c / \rho_c)^{1/6}} \cdot \frac{u^{1/2}}{d_p^{1/2}} \quad (13)$$

The first term in Equation (13) is a function of pressure and temperature, and the second term is a function of flow conditions.

The internal mass transfer coefficient of the droplet, k_{ci} , can be estimated using the following equation (McCabe et al., 1993):

$$k_{ci} = \frac{10D_v}{D_p} \quad (14)$$

The diffusivity, D_v , in Equation (14) depends on the concentration of the solutes and changes significantly during the solidification process, especially when the solute concentration reaches supersaturation or the liquid phase viscosity increases prior to solidification.

A small droplet size is known to promote the formation of dense particles (Jayanthi et al., 1993; Che et al., 1998). The decrease in the droplet size increases the mass transfer coefficient inside the droplet (Equation 14; $k_{ci} \sim d_p^{-2}$) more than the mass transfer coefficient on the droplet interface (Equation 13; $k_c \sim d_p^{-0.5}$). Therefore, small microspheres are usually more compact than large microspheres, because a high concentration gradient is not formed inside the solidifying droplet.

Different approaches have also been used to monitor and determine the solidification degree of microspheres. Jeyanthi et al. (1996) evaluated the solvent removal and the solidification degree of the microspheres by taking samples from the microsphere preparation vessel during the solidification. Legrand et al. (1995) studied the kinetics of the solidification by following the diffuse reflectance of the dispersed phase. Yang et al. (2000a) determined the shrinkage rate of the microspheres during the evaporation step. Mateovic et al. (2005) lowered the stirring speed at pre-defined times during the solidification step and monitored whether the size of the microspheres was affected by the change in the stirring speed. Katou et al. (2008) monitored and modeled the solidification degree of the microspheres during the preparation process. Jayanthi et al. (1993) studied the effect of various parameters on a microsphere formation by solute precipitation. A comparison of the characteristic time constants demonstrated that the droplet shrinkage and the solute diffusion were the slowest processes. The fastest processes, i.e. the vapor diffusion, and the heat conduction in the gas phase and in the liquid phase, can be assumed to reach the steady state. High initial concentrations and low ambient temperatures were demonstrated to favor the formation of dense microspheres. Im et al. (2005) noticed that the hollow cores formed inside polystyrene particles (prepared using solvent evaporation) were larger when toluene was used as a solvent compared to those made using styrene as a solvent. Toluene has a higher vapor pressure than styrene: the boiling point of toluene and styrene are 111°C and 145°C, respectively. The stronger

flux of the toluene compared to styrene led to the formation of holes with larger openings.

The porosity of the matrix can be a desired property of microspheres. For example, by increasing the porosity, the degradation rate of the microsphere matrix increases and therefore the drug release rate can be improved. The porosity of microspheres can be increased for example by adding a non-solvent, which does not dissolve the matrix material, in the dispersed phase (Hong et al., 2005; Ahmed and Bodmeier, 2009). Then the dispersed phase contains the matrix material, a good solvent, and the non-solvent. During the solidification the added non-solvent stays in the solidifying droplet forming a porous structure. The pore size can be adjusted by changing the volume ratio of the non-solvent to the good solvent, the matrix concentration, and also the stirring speed (Hong et al., 2005).

The surface porosity of microspheres has been shown to increase at preparation temperatures close to the boiling point of the dispersed phase solvent (Fu et al., 2005). The reason for the increased porosity at high temperatures was explained as the faster evaporation rate of the solvent in comparison to that at low temperatures. In the author's opinion, another reason for the increased porosity at high temperatures could be the increased solubility of the continuous phase in the dispersed phase with increasing temperature; therefore more continuous phase was embedded in the solidifying droplet, forming more porous microspheres.

Porous microspheres can also be produced using a multiple emulsion solvent extraction/evaporation method. A porous matrix is formed as a result of inner water embedded in the dispersed phase (w/o/w-emulsion; Yang et al., 2000a). The porosity and the pore size can be controlled by adjusting the volume ratio of the internal aqueous phase to the oil phase: the higher the volume ratio of the phases, the more porous microspheres are formed (Yang et al., 2000b). The porosity has been seen to decrease with increasing polymer concentration (Mao et al., 2007; Schlicher et al., 1997; and Yang et al., 2001). The viscosity of the dispersed phase increases as the polymer concentration increases. Therefore, the inner aqueous phase droplets coalesce less and the porosity of the microspheres decreases. The porosity of the microspheres can also be adjusted by adding salt or sugar in the internal or external aqueous phase (w/o/w-emulsion). An osmotic gradient is created between the aqueous phases as a result of the salt or sugar addition. This osmotic gradient causes water to flow from the internal aqueous phase to the external aqueous phase when the salt or the sugar is added to the external aqueous phase, and therefore the porosity of the microspheres decreases (Jiang et al., 2002; Wang and Guo, 2008; Wang

2010). A higher osmotic pressure resulted in a denser internal structure (Jiang et al., 2002). The porosity of microspheres has been increased by adding salt in the internal aqueous phase (Ahmed and Bodmeier, 2009). The presence of salt in the internal aqueous phase resulted in water flux from the outer aqueous phase to the inner aqueous phase. The entrapped water droplets evaporated during the drying process, leaving pores behind.

It is also possible to produce porous microspheres by adding a gas foaming agent, such as ammonium bicarbonate, in the internal aqueous phase (Kim et al., 2006). Ammonium bicarbonate released carbon dioxide and ammonia gas during the solvent evaporation step resulting in the formation of pores. The pore diameter of the microspheres increased as the ammonium bicarbonate concentration rose.

3. METHODS

3.1 Preparing microspheres

Methylaluminoxane microspheres were prepared using an emulsion based solvent extraction method. In Publication I a design of experiments (DOE) approach was performed using Modde 7.0 to investigate also the combined effects of the studied parameters on the microsphere properties. In Publications II-V the effect of one process parameter at time on the microsphere properties was investigated. The detailed microsphere preparation conditions are presented in Publications I-V. Methylaluminoxane (MAO) was used as the matrix material of the microspheres and toluene as a solvent. At first a hydrocarbon-in-perfluorocarbon emulsion was formed in a stirred vessel. The emulsification vessel (made from glass) was baffled. An anchor-type stirrer was used to mix the phases (the stirrer element was made from Teflon; diameter 3.9 cm). A surfactant was used to stabilize the emulsion. The emulsion was stirred for 15 min. The following emulsification parameters were studied: the emulsification temperature, the surfactant concentration, the stirring speed, the matrix material concentration of the dispersed phase (= the dispersed phase viscosity), the continuous phase viscosity, and the volume ratio of the dispersed to the continuous phase. The solvent from the dispersed phase was extracted into the continuous phase by mixing the emulsion with an excess of perfluorocarbon. Therefore, solid microspheres were produced. Two different solidification strategies were used to solidify the emulsion droplets: I) the emulsion was added into the excess of the perfluorocarbon (Publications I-III; Figure 3) and II) the excess of the perfluorocarbon was added into the emulsion (Publications IV-V; Figure 4). With the preparation method I, approximately one quarter of the emulsion was solidified so that the solidification conditions, i.e. temperature and toluene concentration, would stay as constant as possible. The following solidification parameters were studied: the emulsion feed velocity in the perfluorocarbon, the temperature of the perfluorocarbon used in the solidification, the addition rate of the perfluorocarbon into the emulsion,

the mixing speed in the solidification vessel, and the solvent concentration in the perfluorocarbon used to solidify the emulsion droplets. After the solidification, the microsphere-perfluorocarbon suspension was cooled to $\sim 30\text{--}40^\circ\text{C}$ or heated to room temperature while stirring, and then the stirring was stopped. After 30 min without mixing, microspheres had settled to the top of the perfluorocarbon. The perfluorocarbon was siphoned out of the vessel. The remaining wet microspheres were dried under an Argon flow at 50°C for two hours. The microsphere yield varied from 0.05 to 0.40 g.

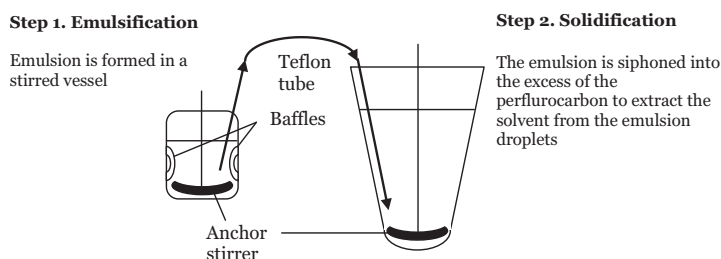


Figure 3. The experimental set-up of preparation method I; the emulsion formed was fed into the excess of the perfluorocarbon.

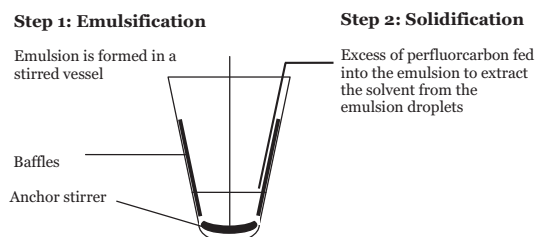


Figure 4. The experimental set-up of preparation method II; the excess of the perfluorocarbon was fed into the emulsion.

3.2 Analytics

3.2.1 Microsphere size analysis

Droplets formed in the emulsification step shrink during solidification because the solvent (toluene) from the droplets is extracted into the continuous phase. Hence, the size of the emulsion droplets is larger than the size of the microspheres.

Microsphere size analysis was performed by dispersing dry microsphere powder (about 20 mg) in oil. Pictures were taken of this dilute suspension using a light microscope. These images were then analyzed using a

software. Only spherical microspheres with a diameter of at least 1 microns were taken into account for microsphere size distribution. Chen and Middleman (1967) have shown from experiment that a minimum count of 300 droplets is necessary to obtain accurate distribution results. Therefore, at least 300 microspheres were included in the microsphere size distribution analysis. Some microsphere batches contained mostly large and highly porous microspheres. Small holes in the matrix material of the microspheres were considered to be small microspheres by the software. To eliminate this error, the microsphere size distribution of these microsphere batches was measured manually.

The microspheres produced were mainly compact but some hollow microspheres were also produced (Publication I); the diameter ratio of the hollow core to the outer diameter of microspheres was about 0.44. The microsphere diameter would decrease only ~3 % if the hollow microsphere formed a compact microsphere (the density of the microsphere matrix is assumed to be a constant). Therefore, the compactness of the microspheres was not taken into account when the mean size of the microspheres was analyzed. The Sauter mean diameter (Equation 3) was used in this thesis to describe the mean size of the microspheres.

3.2.2 Microscopy

A scanning electron microscope (FEI Quanta 200) was used to determine the microsphere shape and the morphology. The microspheres were mounted on metal stubs with double-sided conductive adhesive tape and coated with gold. The coating was performed under an inert atmosphere. Microspheres were cut with a knife before coating to see the morphology inside the microspheres. SEM imaging was performed using an electron beam energy of 3 keV.

The size and morphology of the microspheres were also analyzed using a light microscope: dry microsphere powder was first dispersed in oil before the pictures were taken of this dilute suspension.

4. RESULTS AND DISCUSSION

4.1 Effect of emulsification conditions on microsphere properties

Data related to the hydrocarbon-in-perfluorocarbon emulsion solvent extraction based microsphere preparation process studied here was lacking. The following emulsification parameters were tested to investigate how these affect the size, the size distribution and the morphology of the microspheres: the surfactant concentration, the tip speed, the emulsification temperature, the volume ratio of the dispersed phase to the continuous phase, the matrix material concentration of the dispersed phase, and the viscosity of the continuous phase.

4.1.1 Effect of surfactant concentration on microsphere properties

The effect of the surfactant concentration on microsphere properties was studied using both microsphere preparation methods (Publications II and IV). The size of the microspheres decreased with increasing surfactant concentration, as expected according to the literature (Mu et al., 2005; Nepal et al., 2007; Rafati et al., 1997). Increased surfactant concentration is known to decrease interfacial tension and hence the droplets break up more easily (Equation 1). Coalescence of droplets is also known to decrease as a result of increased surfactant concentration, resulting in a decrease in the size of the microspheres.

The Sauter mean diameter of the microspheres decreased exponentially as the surfactant concentration increased with preparation method I (Figure 5A). The microsphere size distribution narrowed with increasing surfactant concentration. The highest surfactant concentration tested was probably close to the critical micelle concentration, because the Sauter mean diameter of the microspheres started to reach a constant value. A further increase in the surfactant concentration after the critical micelle

concentration does not reduce the interfacial tension and therefore the microsphere size does not decrease further (see Chapter 2.1.2). Nepal et al. (2007) reported a similar trend in the size of microspheres as surfactant concentration was increased. Mu et al. (2005) and Rafati et al. (1997) reported that the mean size of the microspheres decreased linearly with increasing surfactant concentration. However, they did not increase the surfactant concentration further to find out whether the mean size of the microspheres would reach a constant value despite increasing surfactant concentration

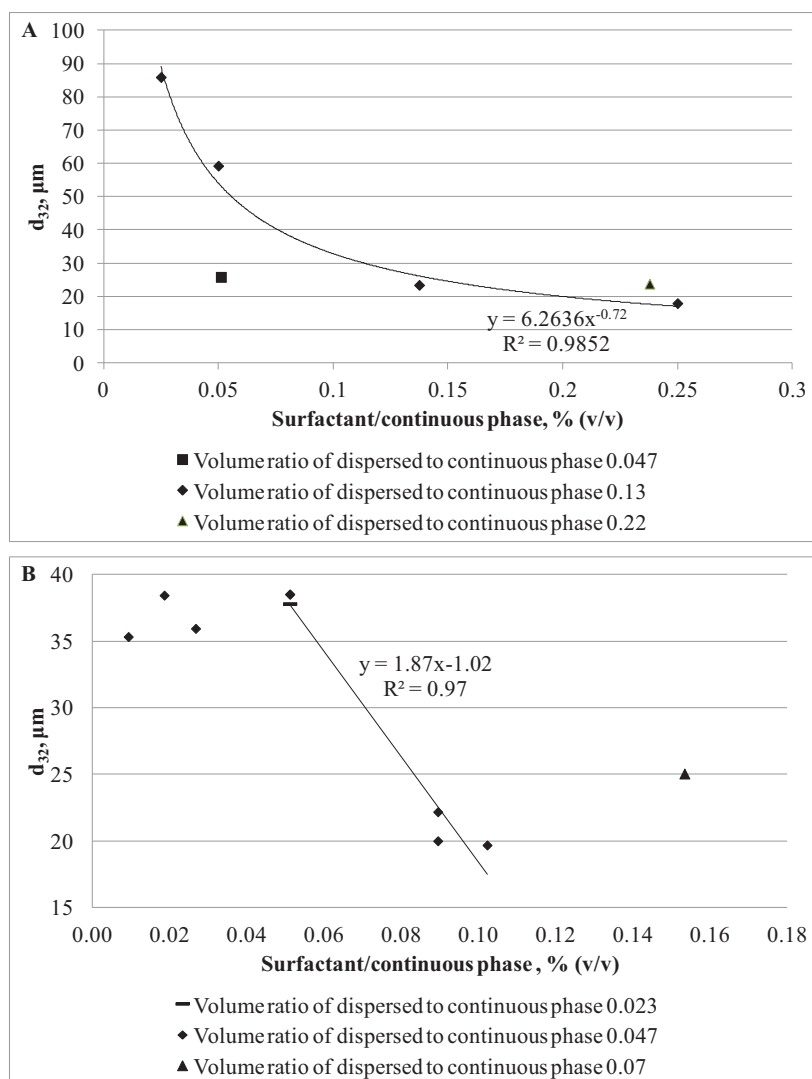


Figure 5. Effect of surfactant concentration on the Sauter mean diameter of microspheres produced using A) the preparation method I (Publication II) and B) the preparation method II (Publication IV).

In the preparation method II, an excess of perfluorocarbon without surfactant was added into the emulsion in order to solidify the emulsion droplets (Publication IV). The increased continuous phase volume decreased both the surfactant concentration and also the volume ratio of the phases. The surfactant concentration was roughly half of the initial value when all the toluene was extracted from the dispersed phase into the continuous phase.

The lowest surfactant concentrations tested were not high enough to stabilize the new liquid-liquid interfaces formed during the droplet break-up with the preparation method I. Therefore, the surfactant addition did not reduce the coalescence of the droplets and the Sauter mean diameter remained almost constant (Figure 5B). A further increase in the surfactant concentration decreased the size of the microspheres significantly; the Sauter mean diameter of the microspheres decreased almost inversely as a function of the surfactant concentration (Figure 5B). In several studies, a similar linear decrease in the mean size of microspheres with increasing surfactant concentration has been observed (Mu et al., 2005; Rafati et al., 1997; Nepal et al., 2007). It is known that a surfactant reduces the interfacial tension between the phases and that the Sauter mean diameter depends inversely on the interfacial tension (Equations 1 and 2). Therefore, the mean size of the microspheres produced using the preparation method II decreased with increasing surfactant concentration as a result of the reduced interfacial tension and coalescence, as with the preparation method I. The highest surfactant concentration tested was probably close to the critical micelle concentration, because the Sauter mean diameter of the microspheres started to reach a constant value with both preparation methods.

Microspheres with the highest tested surfactant concentration (produced using preparation method I) were more compact according to the light microscopy images (Figures 4A-D in Publication II) than the microspheres prepared using lower surfactant concentrations. One reason for the higher compactness at a high surfactant concentration was the small size of the microspheres, which is known to result in the formation of more compact microspheres. A high surfactant concentration is known to slow down mass transfer, which also promotes the formation of compact microspheres (Che et al., 1998; Zhou et al., 2001). The surfactant concentration had no significant effect on the morphology of the microspheres produced with preparation method II. Mainly compact microspheres were produced with all the surfactant concentrations tested.

4.1.2 Effect of stirring speed on microsphere properties

The effect of the stirring speed and the Weber number on microsphere properties was studied using both microsphere preparation methods (Publications II and IV).

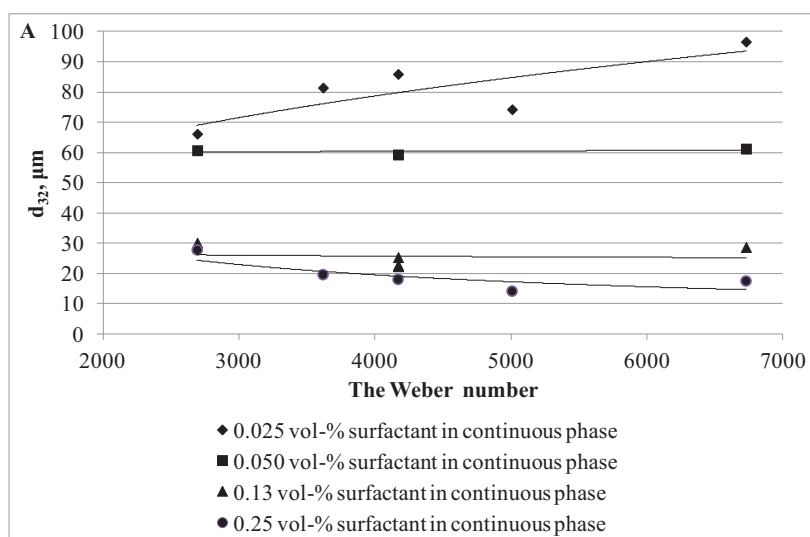
The size of the microspheres produced with the preparation method I (Publication II) decreased with increasing stirring speed at a high surfactant concentration, in accordance with the literature (Mu et al., 2005; Gabor et al., 1999; Mateovic et al., 2002; Nepal et al., 2007; Jégat et al., 2000; Bahukudumbi et al., 2004). Greater shear forces were created as the stirring speed was increased (Equations 1 and 2); therefore, smaller microspheres were produced with increasing stirring speed. However, an increase in stirring speed increased the Sauter mean diameter of the microspheres at the lowest tested surfactant concentration (Publication II) as the coalescence of droplets increased more than the break-up of droplets. This also coincided with a broadening of the size distribution. At high surfactant concentrations, the stirring speed did not have a significant effect on the broadness of the size distribution.

As expected, the size of the microspheres produced with the preparation method II (Publication IV) also decreased with increasing stirring speed. The Sauter mean diameter of the microspheres decreased from $\sim 41\ \mu\text{m}$ to $\sim 23\ \mu\text{m}$ as the stirring speed increased from 450 rpm to 500 rpm. The bulk mixing at the slowest stirring speed tested (450 rpm) was not intense enough to keep the solidifying droplets well dispersed in the bulk emulsion during the microsphere preparation leading to large droplets. The stability of the studied hydrocarbon-in-perfluorocarbon emulsion was poor, partly due to the high density difference between the phases. The bulk mixing was enhanced when the stirring speed was increased from 450 rpm to 500 rpm. Hence the droplet coalescence reduced and significantly smaller microspheres were produced. A further increase in the stirring speed from 500 rpm to 600 rpm led to a smaller decrease in the mean size of the microspheres compared with the increase in stirring speed from 450 to 500 rpm. The microsphere size distribution narrowed significantly as the stirring speed increased. A similar trend in the microsphere size distribution was also seen by Gabor et al. (1999).

A good agreement between the Sauter mean diameter of the microspheres and the fitted Weber number was found (Equation 2; Figures 6A-B). In the Weber number calculations, the interfacial tension of the toluene-PFC system was used. A surfactant is known to reduce interfacial tension, hence the interfacial tension value used in the calculations was probably too high. The interfacial tension changes the constant in the correlation between the

Sauter mean diameter and the Weber number (Equation 2) but does not affect the exponent value in the correlation. The theoretical exponent for a non-coalescing and fully turbulent system is -0.6 (Equation 2). In the preparation method I, the emulsion was added into the continuous phase through a tube in which the flow was laminar. The Weber number in the siphoning tube was significantly lower than during the emulsification.

As expected, the size of the microspheres produced with the preparation method I at a high surfactant concentration decreased when the Weber number increased (Figure 6A). An exponent value of -0.56 (see Equation 2), close to the theoretical value (-0.6), was achieved when microspheres were produced with the preparation method I. One reason for the deviation from the theoretical value was that some of the experiments were done in a transient flow. In addition, the emulsion studied was a coalescing system. Bahukudumbi et al. (2004) reported a smaller exponent value, -0.53, than was observed with preparation method I, however, no explanation for the deviation from the theoretical value was offered. A relatively similar exponent value, -0.72, in the correlation between the Sauter mean diameter of the microspheres and the Weber number was presented by Mu et al. (2005). They considered transient flow conditions to be the reason for the deviation from the theoretical value.



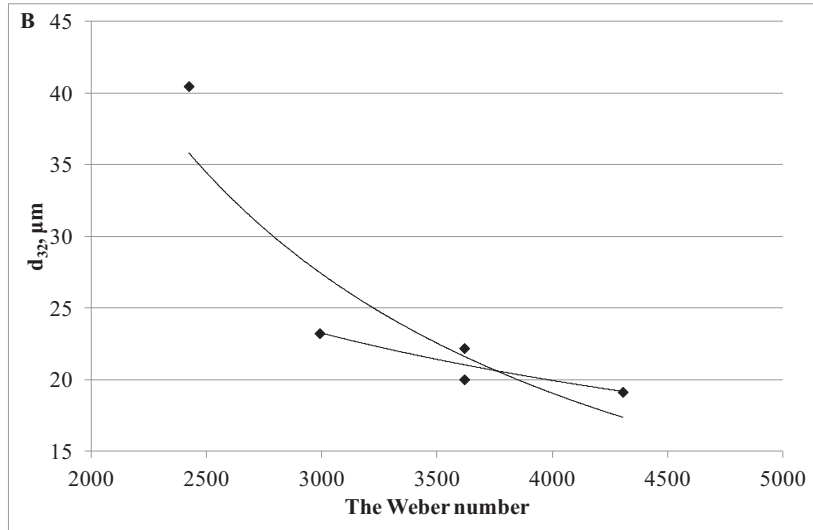


Figure 6. Effect of the Weber number on the Sauter mean diameter of microspheres produced using A) the preparation method I (Publication II), and B) the preparation method II (Publication IV). The preparation method I: volume ratio of the phases 0.125. The preparation method II: volume ratio of the phases 0.047 and 0.09 vol-% surfactant concentration in the continuous phase; two curve fittings: I) including all data points, and II) excluding the data point achieved using the slowest stirring speed.

Contrary to the result obtained at a high surfactant concentration, the Sauter mean diameter of the microspheres produced with preparation method I (Publication II) increased with an increasing Weber number at low surfactant concentrations (Figure 6A). The exponent value (Equation 2) with the lowest tested surfactant concentration was positive, 0.33. The reason for this was that the coalescence of droplets increased more than the break-up of droplets when the Weber number increased. Jafari et al. (2008) discussed this similar phenomenon in a review article and several authors have reported that the mean droplet size increases with increasing mixing intensity during high-pressure emulsification.

A surfactant concentration was found at which the emulsification conditions did not affect the Sauter mean diameter of the microspheres produced with the preparation method I, although the Weber number varied from 2700 to 6700 (Figure 6A). Hence a stable droplet size region was found. Church and Shinnar (1961) described the interrelationship between suspension, break-up, and coalescence of droplets. A stable region exists in the center area (droplet size was presented as a function of stirring speed) bounded by the three lines representing the droplet break-up, droplet coalescence, and suspension phenomena. A balance between droplet break-up and coalescence was established inside the bounded region. Outside this stable region either droplet break-up or coalescence dominates until the break-up or the coalescence line is reached, respectively.

The Sauter mean diameter of the microspheres produced using the preparation method II (Publication IV) decreased exponentially as the Weber number increased (Figure 6B). Higher shear forces were produced to break up the droplets as the Weber number increased and led to a decrease in the mean size of the microspheres (Equations 1 and 2). These experiments were done in fully turbulent conditions. The exponent value (Equation 2) for the preparation method II was -0.53, when the slowest stirring speed tested (450 rpm) was not considered (Figure 6B). That exponent value was the same as that reported by Bahukudumbi et al. (2004). The observed exponent value was also close to the theoretical value and the value obtained with the preparation method I (Publication II). It was assumed that the bulk mixing was not intense enough to maintain complete dispersion during the solidification at the slowest tested stirring speed (450 rpm). The exponent value was -1.26 (Figure 6B) when all data points were included, which was significantly higher than the theoretical exponent value.

The stirring speed had no significant effect on the microsphere morphology and compactness according to the SEM images.

4.1.3 Effect of matrix concentration of dispersed phase on microsphere properties

The effect of the matrix material concentration of the dispersed phase on microsphere properties was studied using both microsphere preparation methods (Publications III and V). The dispersed phase viscosity decreased with decreasing matrix material concentration. Other emulsification parameters were kept constant.

The effect of the MAO (= matrix material) concentration on the viscosity of the dispersed phase was measured at 0°C and 22°C (Figure 7A). The viscosity of the MAO solution starts to increase significantly between 30 and ~37 wt-% MAO, indicating the formation of gels in that range. The gelation concentration of the MAO solution is higher at lower temperatures according to the measured data. A high temperature is known to favor the formation of gels in MAO solution; MAO is recommended to be stored at -20°C to prevent gel formation.

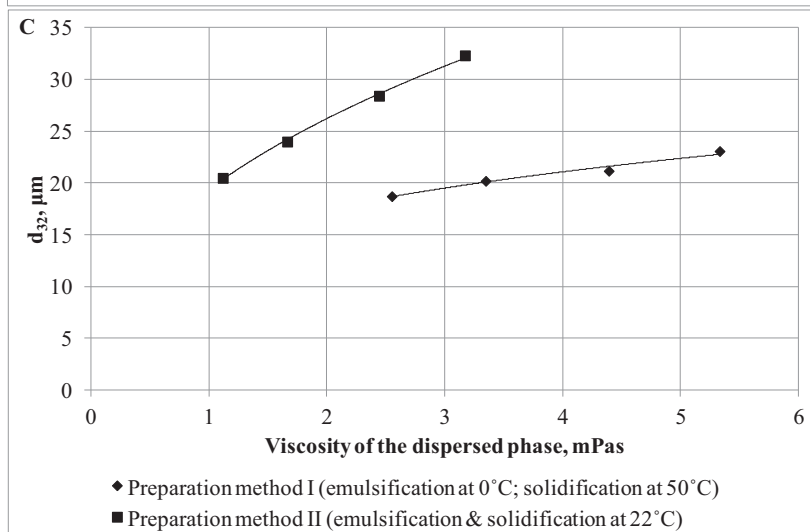
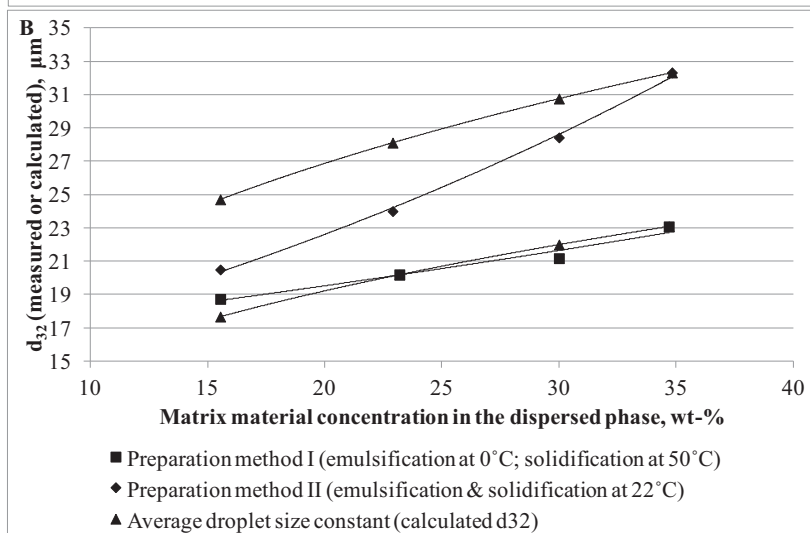
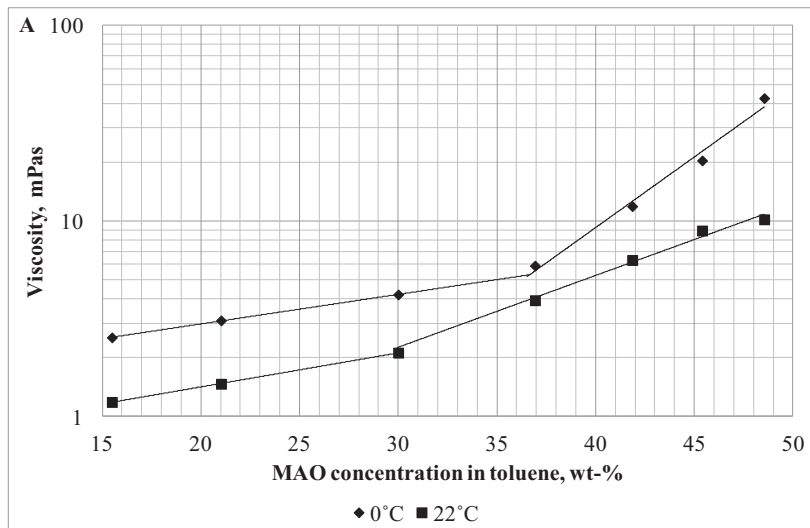


Figure 7. A) Viscosity of MAO solution as a function of MAO concentration in toluene, wt-%. B) The effect of the matrix material concentration on the Sauter mean diameter of the microspheres (measured and calculated) produced using the preparation methods I and II. C) The Sauter mean diameter of the microspheres as a function of the dispersed phase viscosity.

The size of the microspheres decreased as the MAO concentration of the disperse phase decreased with both preparation methods (Figure 7B), in accordance with the literature (Yang et al., 2000b; Yang et al., 2001; Badri Viswanathan et al., 1999; Rafati et al., 1997; Nepal et al., 2007; Gabor et al., 1999; Mao et al., 2008; Choi et al., 2002; D'Aurizio et al., 2011). The dispersed phase viscosity decreased as the MAO concentration decreased. Therefore, the droplets broke up more easily at the same mixing intensity and hence smaller microspheres were produced at lower MAO concentrations.

A calculation was done to assess if the size of the microspheres was affected only by the MAO concentration of the dispersed phase. The calculation was based on two assumptions: 1) the emulsion droplet size would be constant, although the MAO concentration in the dispersed phase changed, and 2) the density of the solid microspheres would be independent on the MAO concentration. According to the calculation the Sauter mean diameter of the microspheres would decrease from 32 to 25 μm as the MAO concentration decreases from 35 to 16 wt-% (the preparation method II) and if the two assumptions above would be valid. However, the measured microsphere size were 32.2 and 20.5 μm produced using MAO concentration 35 and 16 wt-%, respectively (Figure 7B; the upper curve). Therefore, the size of the microspheres produced using the preparation method II was also affected by the viscosity of the dispersed phase and not only by the both the MAO amount in the droplet. On the other hand, the calculation indicated that the Sauter mean diameter of the microspheres produced using the preparation method I was mainly affected by the MAO amount in the droplet, not by the viscosity of the dispersed phase (Figure 7B; the lower curve).

The measured Sauter mean diameters of the microspheres were used to fit the coefficient and the exponent of the empirical Equation (4). A good correlation between the measured Sauter mean diameter and the viscosity of the dispersed phase was observed (Figure 7C). The fitted exponent values of the empirical Equation (4) were 0.27 (the preparation method I) and 0.44 (preparation method II). The exponent value achieved with the preparation method I was close to the value, 0.25, presented by Calderbank (1958). Maa et al. (1996b) found that the droplet size was proportional to $\mu_d^{0.22}$ when the emulsifications were done in a baffled tank. Other values for the exponent have been presented in the range of 0.004 to 0.40 depending on the system used (Maa et al., 1996a,c; Urban et al., 2006). Badri

Viswanathan et al. (1999) reported that particle size was directly proportional to polymer solution viscosity.

No significant effect of the matrix material concentration of the dispersed phase on the microsphere size distribution and morphology was seen.

4.1.4 Effect of continuous phase viscosity on microsphere properties

The effect of the continuous phase viscosity on microsphere properties was studied using the preparation method I (Publication III). The viscosity of the continuous phase used in emulsification was increased by adding a viscosity increasing agent to the continuous phase. The viscosity of the PFC used in the solidification was not changed.

The size of the microspheres decreased as the viscosity of the continuous phase increased (Figure 8). An increase in the continuous phase viscosity extended the film drainage time between droplets, decreasing the probability of coalescence (see Chapter 2.1.1) and, as a consequence, forming smaller microspheres.

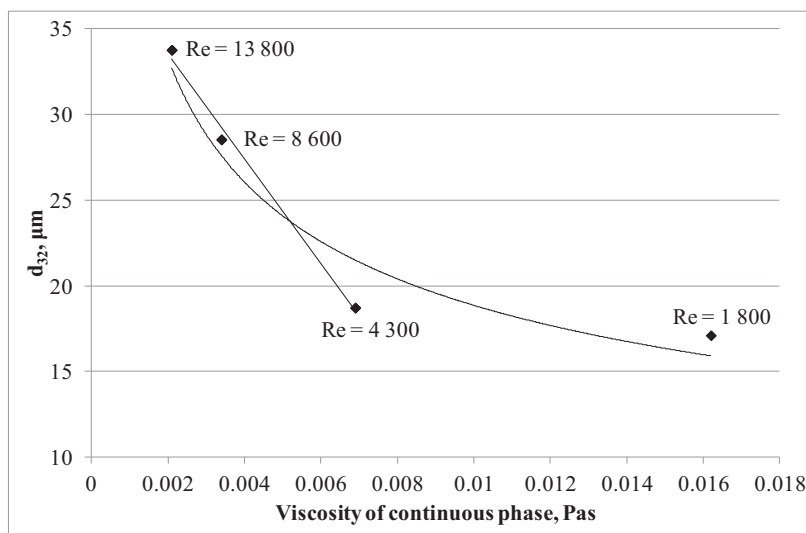


Figure 8. The Sauter mean diameter of the microspheres as a function of continuous phase viscosity (continuous phase viscosity in the emulsification step only was varied). The microspheres were prepared using the preparation method I (Publication III). Re indicates the Reynolds number in the emulsification vessel.

A good linear correlation between the Sauter mean diameter of the microspheres and the continuous phase viscosity was seen when the experiment done in laminar flow conditions (the highest tested continuous phase viscosity, ~ 0.016 Pas) was not considered (Figure 8). In this case, the Sauter mean diameter of the microspheres decreased linearly as a function of the continuous phase viscosity at a range of continuous phase viscosity from ~ 0.002 to ~ 0.007 Pas ($R^2 = 0.9929$). Those experiments were

performed in transient or fully turbulent conditions and, therefore, a better correlation was observed.

The addition of the viscosity increasing agent increased both the density and the viscosity of the continuous phase thereby affecting the Reynolds number. The change in the Reynolds number was affected mainly by the continuous phase viscosity rather than the density. A correlation between the Sauter mean diameter of the microspheres and the Reynolds number in the emulsification step was observed. Microspheres with a smaller Sauter mean diameter were produced under laminar conditions compared to microspheres produced under fully turbulent conditions: the Sauter mean diameter decreased almost linearly with the Reynolds number (see Figure 5B in Publication III) from ~ 34 to ~ 17 μm , when the Reynolds number decreased from 13800 to 1800 due to the viscosity increasing agent addition. The coalescence of droplets decreased because the Reynolds number decreased and the continuous phase viscosity increased; hence the size of the microspheres decreased. The microsphere size distribution narrowed, as the increased viscosity of the continuous phase decreased the coalescence of droplets.

A correlation between the Sauter mean diameter and the Weber number was used to predict the size of the microspheres. The Sauter mean diameter of the microspheres was calculated by combining Equations (2) and (4), and assuming that the Sauter mean diameter is a constant fraction of d_{max} (Sprow, 1967).

$$\frac{d_{32}}{D} = a \cdot We^b \cdot \left(\frac{\mu_d}{\mu_c} \right)^d \quad (15)$$

The calculated values were fitted using Equation (15) with the measured values and a good correlation was seen between the measured and fitted values (Figure 5C in Publication III). In the Weber number calculations, the interfacial tension between toluene and perfluorinated polyether-PFC was used. The addition of a surfactant reduces interfacial tension and hence the calculated Weber numbers are too low. However, a change in the interfacial tension has little effect on the value of exponent b and only changes the proportionality coefficient, a , in the correlation between the Sauter mean diameter of the microspheres and the Weber number (see Equations 1 and 2). The fitted value of exponent b in Equation (15) was -0.50, which was close to the values -0.56 and -0.53 observed in the previous tests (see Chapter 4.1.2). The theoretical value of that exponent is -0.6 and is given for a turbulent flow and a dilute non-coalescing system. The fitted value was close to the theoretical value although two experiments were done under transient flow conditions and one experiment was done under laminar flow conditions. The fitted value of the exponent d in Equation (15)

was 0.41. This was close to the value presented by Maa et al. (1996b). They found that the droplet size was proportional to $(1/\mu_c)^{0.42}$ when the experiments were done in a baffled tank. The droplet size has been found to be proportional to $(1/\mu_c)^{0.02-0.56}$ depending on the system used (see Chapter 2.1.2).

4.1.5 Effect of volume ratio on microsphere properties

The effect of the volume ratio of the phases on the microsphere was studied using both microsphere preparation methods (Publications III and IV). A smaller dispersed phase volume creates fewer droplets, therefore, less surface area is created requiring stabilization during the emulsification if the droplet size distribution remains constant. Therefore, the surfactant concentration in the continuous phase was varied so that the volume ratio of the surfactant to the dispersed phase was constant when the effect of the volume ratio of the phases on the microsphere was studied.

The Sauter mean diameter of the microspheres was not only affected by the volume ratio of dispersed to continuous phase but also by the surfactant concentration. The Sauter mean diameter of microspheres produced with both preparation methods (I and II) decreased first when the volume ratio of phases was increased (Publications III and IV). A further increase in the volume ratio of the phases increased the Sauter mean diameter of the microspheres. A similar effect of the volume ratio of the phases on microsphere size has been reported (Gabor et al., 1999). However, they did not give an explanation for the observed result.

With the preparation method I the size of the microspheres decreased from ~26 to ~21 microns when the volume ratio of the phases increased from 0.04 to 0.13. The volume ratio of surfactant to dispersed phase was kept constant. Therefore, the surfactant concentration in the continuous phase increased when the volume ratio of the phases increased (Figure 5A). The increased surfactant concentration reduced interfacial tension and hence smaller microspheres were produced although the volume ratio of the phases increased. The Sauter mean diameter of the microspheres increased from ~21 to ~24 microns when the volume ratio of the phases was further increased from 0.13 to 0.22. As a result of the increased volume ratio of the phases the surfactant concentration increased from 0.14 to 0.24% (v/v) because the volume ratio of the surfactant to the dispersed phase was kept constant. Coalescence of the droplets increased as a result of increased volume ratio of the phases. The effect of this was larger than the increased surfactant concentration, therefore, larger microspheres were produced. With the preparation method I no significant effect of the volume

ratio of the dispersed to the continuous phase on the microsphere size distribution was observed.

The size of the microspheres produced with the preparation method II remained almost the same, 38 microns, as the surfactant concentration was 0.05 % (v/v) although the volume ratio of the phases varied from 0.023 to 0.047. In conclusion, the size of the microspheres was not affected by the volume ratio of the phases at surfactant concentration of 0.05 % (v/v). The size of the microspheres produced with the preparation method II decreased from ~38 to ~20 microns when the volume ratio of the phases increased from 0.023 to 0.047. The surfactant concentration was 0.05 % (v/v) at a volume ratio of 0.023 and 0.10 % (v/v) at a volume ratio of 0.047. The increased surfactant concentration reduced the interfacial tension and hence smaller microspheres were produced even though the volume ratio of the phases increased. Therefore, at a low volume ratio of the phases (less than 0.047) the size of the microspheres was primarily affected by the surfactant concentration as opposed to the variation in the volume ratio of the phases. The Sauter mean diameter of the microspheres produced with the preparation method II increased from ~20 to ~25 microns when the volume ratio of the phases was further increased from 0.047 to 0.070. The surfactant concentration was 0.10% (v/v) at a volume ratio of 0.047 and 0.15% (v/v) at a volume ratio of 0.070. Despite the increased surfactant concentration the size of the microspheres increased as the volume ratio of the phases increased. The effect of the volume ratio of the phases on the size of the microspheres became more significant than the effect of the surfactant at high volume ratio of the phases. According to Equation (7) and experimental results (Jeffery et al., 1993; Ellis and Jacquier 2009) the size of the microspheres is expected to increase with the increasing volume ratio of the phases. The main explanation for the increased microsphere size is the turbulence dampening caused by the increased volume ratio of the phases. Additionally, the number of collisions should increase as the volume ratio of the phases increases, thus increasing the size of the microspheres.

With the preparation method I, the Sauter mean diameter of the microspheres decreased exponentially as a function of the volume ratio of surfactant to dispersed phase even though a different volume ratio of the phases was used (Figure 9). The result indicated that the surfactant affected the microsphere size mainly by preventing the coalescence of the droplets as opposed to decreasing the interfacial tension in this studied system. With the preparation method I, no correlation between the Sauter mean diameter of microspheres and the surfactant concentration in the

continuous phase was seen when the volume ratio of the phases was varied, as was observed with the preparation method II.

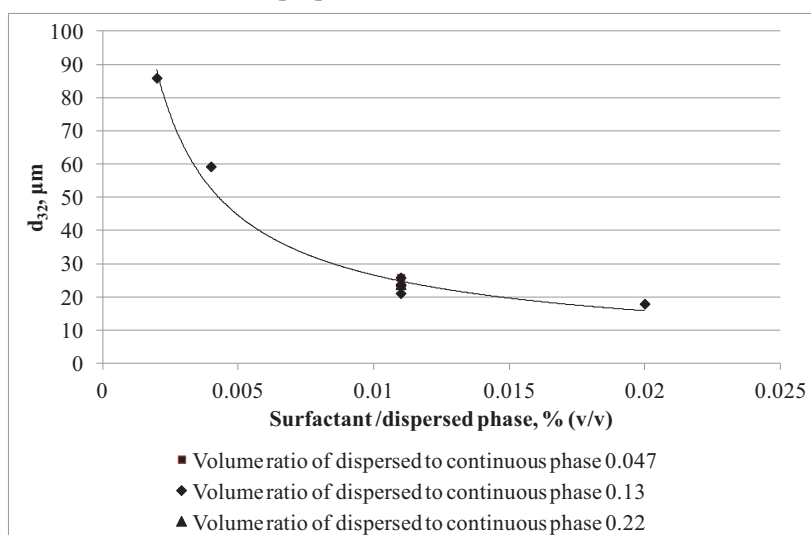


Figure 9. The Sauter mean diameter of the microspheres as a function of the volume ratio of surfactant to dispersed phase with different surfactant concentration in the continuous phase and volume ratio of the phases. The microspheres were produced using preparation method I (Publication III).

The volume ratio of the phases had an effect on the morphology of the microspheres produced using the preparation method II according to the SEM images (see Figures 6A-C in Publication IV). The majority of microspheres were compact spheres with all tested volume ratios of the phases. However, the surfaces of the microspheres produced with a high volume ratio of phases were not as smooth as those produced with the low volume ratios of the phases. The formation of the non-smooth surfaces was probably linked to the higher toluene volume and/or the surfactant concentration. The addition rate of the perfluorocarbon to the emulsion was set so that the time needed to extract all toluene from the dispersed phase into the continuous phase was constant in all volume ratio experiments. Therefore, the toluene extraction rate was the highest at high volume ratios of the phases which could explain the observed change in the surface morphology of the microspheres. The solidification rate had no significant effect on the surface morphology of the microspheres when the volume ratio of the phases was lower, 0.047. Another possible reason for the formation of a non-smooth surface could be the high surfactant concentration (0.15% (v/v)) at the highest volume ratio of the phases. The surfactant concentration had no significant effect on the microsphere morphology when the surfactant concentration was less than 0.10% (v/v) at a volume ratio of phases 0.047. The surface viscosity of the droplets is known to increase with increasing surfactant concentration especially after

the critical micelle concentration (Leng and Calabrese, 2004). With the increased surface viscosity, the deformed droplet (deformation caused by shear forces) did not return back to the thermodynamically more favorable spherical shape. Therefore, the microspheres had rough surfaces at high surfactant concentration with a high volume ratio of the phases. A high surfactant concentration is also known to reduce the mass transfer so the droplet viscosity increases slowly and the droplet is exposed to shear forces for longer. Mateovic-Rojnik et al. (2005) noticed that the particle surface roughness increased with decreasing solidification rate.

4.1.6 Effect of temperature on microsphere properties

The effect of temperature on the properties of the microspheres was studied using both microsphere preparation methods (Publications II and V). The temperature of the emulsion changed slightly during the emulsification step. The solubility of toluene in PFC is strongly affected by temperature. A small decrease in the emulsification temperature results in the formation of small toluene droplets in the continuous phase (toluene saturated PFC), because the toluene solubility in the continuous phase decreases. As a result of this, the continuous phase becomes cloudy. A small increase in the emulsification temperature increases the toluene solubility in the PFC phase and the small toluene droplets are extracted into the PFC phase. Droplet size and droplet size distribution are therefore affected by a small temperature change.

In theory, a higher temperature reduces the viscosity of the emulsion phases and lowers the interfacial tension, thereby reducing the energy needed to create smaller droplets (Equation 1). However, an increase in the emulsification temperature resulted in the formation of larger microspheres at low surfactant concentration. The higher emulsification temperature increased the coalescence of the droplets and, hence, the size of the microspheres increased with increasing temperature (preparation method I; Publication II). Nepal et al. (2007) and Yang et al. (2000a) reported a similar trend. However, they gave a different explanation for the increased microsphere size: the solidification process was faster at the higher temperature and consequently the droplets were affected by the stirrer shear forces for a shorter time before solidification. At high surfactant concentration, the effect of the emulsification temperature on the Sauter mean diameter of the microspheres was not as significant as at low surfactant concentrations. The size distribution of the microspheres produced at low surfactant concentrations widened with increasing temperature as a result of increased coalescence. A similar trend was also

reported by Mateovic-Rojnik et al. (2005) and Yang et al. (2000a). At high surfactant concentrations, the temperature did not have a significant effect on the microsphere size distribution.

The preparation temperature (both the emulsification temperature and the temperature of the PFC added to the emulsion were varied) significantly affected the Sauter mean diameter of the microspheres produced with preparation method II (Publication V). The Sauter mean diameter of the microspheres produced at 22°C and 30°C were almost the same, roughly ~22 µm. The microsphere size distribution of both batches was also similar. However, a further increase in the preparation temperature to 40 and 50°C significantly increased the size of the microspheres: the Sauter mean diameter was ~31 and ~70 µm respectively were produced. The size distribution of the microspheres prepared at 50°C was significantly broader compared to batches prepared at low temperatures. The Weber number increases with increasing temperature and that should result in the formation of smaller droplets and hence the formation of smaller microspheres (Equation 1). However, an opposite trend was observed: the size of the microspheres increased with increasing temperature. As the preparation temperature increases the viscosity of the continuous phase decreases leading to increasing coalescence of the droplets as the film drainage rate increased and hence larger microspheres with broader size distribution were produced. Mateovic-Rojnik et al. (2005) and Yang et al. (2000a) also reported that the average size of the microspheres increased with increasing preparation temperature. However, a different explanation for the increased microsphere size was offered by Mateovic-Rojnik et al. (2005): the solidification process was faster at high temperatures and consequently the droplets were affected by the stirrer shear forces for a shorter time before solidification. In the experiments presented in Publication V, increased coalescence was thought to be the main reason for the increased size of the microspheres as the preparation temperature increased. In addition, the gel formation of the MAO affected the size of the microspheres. The dispersed phase matrix material, MAO, is known to form gels as a function of time and temperature; heat increases the gel formation rate of MAO. As the preparation temperature of the microspheres increased, the gel formation of the MAO also increased. Therefore, the viscosity of the dispersed phase increased and this could also contribute the formation of larger microspheres at higher preparation temperatures.

The effect of temperature on the morphology of the microspheres is discussed in Chapter 4.2.3.

4.2 Effect of solidification conditions on the microsphere properties

The effects of the solidification conditions on the properties of the microspheres were investigated. Two different solidification methods were used to solidify the droplets: I) the emulsion was added into the excess of perfluorocarbon (Publications I-III) and II) the excess of the perfluorocarbon was added into the emulsion (Publications IV and V). Both hollow and compact microspheres were produced with the preparation method I. Mainly dense microspheres were produced with the preparation method II.

4.2.1 Preparation method I: Emulsion added into excess of perfluorocarbon

The solidification parameters studied with the preparation method I were the temperature of the perfluorocarbon used in the solidification step, the emulsion feed velocity in the perfluorocarbon used in the solidification step and the mixing speed in the solidification step (Publication I).

Temperature

A change in the solidification temperature affected the Sauter mean diameter of the microspheres: the Sauter mean diameters of the microspheres obtained at 90°C were larger than those obtained at 10°C. This was partly because the microspheres solidified at 90°C had a hollow core and the microspheres solidified at 10°C were mainly dense. Nepal et al. (2007) and Yang et al. (2000a) also reported that the size of the microspheres increased with an increasing preparation temperature. The solidification process was faster at high temperatures and consequently the droplets were affected by the stirrer shear forces for a shorter time before solidification.

Flow conditions in the solidification vessel

Solidification of methylaluminoxane droplets was performed in an unbaffled vessel and as a result, a swirling flow pattern was formed in the solidification vessel. The emulsion was transferred into the excess of perfluorocarbon directly downwards, so the emulsion flow into the solidification vessel and the perfluorocarbon flow in the solidification vessel were mixed as in a T-mixer. The emulsion addition velocity, $u_{e,f}$, and the tip speed, u_{ts} , were combined to obtain the combined emulsion velocity, $u_{e,c}$:

$$u_{e,c} = \sqrt{u_{e,f}^2 + u_{ts}^2} \quad (16)$$

Correlations were found at 10°C and 90°C between the Sauter mean diameter of the microspheres and the combined emulsion velocity (Figure 4 in Publication I): the higher the combined emulsion velocity, the smaller the microspheres formed. According to Equation (1), the droplet size depends on (flow velocity)². Therefore, the measured Sauter mean diameter of the microspheres was plotted as a function of (combined emulsion velocity)² (see Equation 1). A good correlation was observed when the slowest combined emulsion velocity was excluded from the fitting (Figure 10). This was done because the mixing conditions were assumed to be inadequate when the combined emulsion velocity was low (less than 0.5 m²/s²), which explained the poor fit to other data points. The fitted exponent values, -0.38 and -0.32, were significantly lower than the theoretical value, -0.6 (Equation 1). For microsphere preparation processes, exponent values of -0.53 (Bahukudumbi et al., 2004) and -0.72 (Mu et al., 2005) have been reported. In the emulsification step the fitted exponent values of the Equation 1 varied from -0.56 to -0.50 (see Chapter 4.1.2). One reason for the deviation between the observed exponent values in the emulsification and the solidification step was the mixing conditions: in the emulsification step the vessel used was baffled whereas in the solidification step the vessel was unbaffled. Therefore, the mixing conditions of the steps differed significantly.

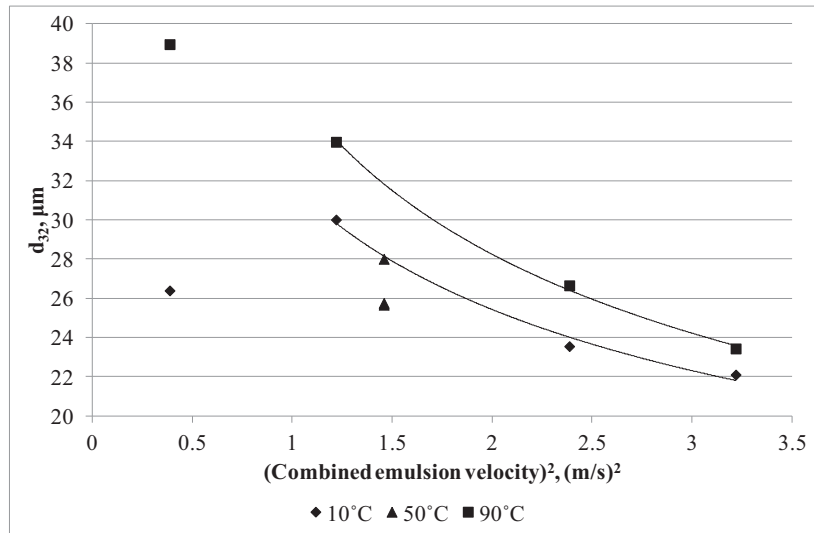


Figure 10. The Sauter mean diameter of the microspheres as a function of (combined emulsion velocity)². The microspheres were produced using the preparation method I (Publication I).

In Publication I, a model was generated for the Sauter mean diameter of the microspheres using a design of experiments program. The validity of the model was good as shown by Figure 5 in Publication I. According to the model, the Sauter mean diameter of the microspheres was affected mainly

by the emulsion addition velocity: the higher the emulsion addition velocity, the smaller the Sauter mean diameter of the microspheres. Raising the solidification temperature was seen to promote an increase in the Sauter mean diameter of the microspheres. Increasing the stirring speed slightly decreased the Sauter mean diameter of the microspheres.

Emulsion transfer time between the emulsification and the solidification step

The stability of the studied hydrocarbon-in-fluorocarbon emulsion was poor. Therefore, the effect of the emulsion transfer time between the emulsification and solidification vessels on the size of the microspheres was studied using the preparation method I (Publication III). One reason for the poor emulsion stability is the high density difference between the phases. However, a significant effect was not seen in the tested time interval (from 0.6 to 1.3 s), although the mixing conditions in the emulsion transfer tube differed greatly to the conditions in the emulsification vessel (Figure 8 in Publication III).

4.2.2 Preparation method II: Excess of perfluorocarbon added into the emulsion

The solidification parameters studied with the preparation method II were the addition rate of the perfluorocarbon (Publication IV) and the temperature of the added perfluorocarbon (Publication V). During the experiments an excess of perfluorocarbon was added into the emulsion in order to solidify the droplets. The increased continuous phase volume affected both the surfactant concentration and the volume ratio of the phases. The surfactant concentration was roughly half of the initial value when all the toluene was extracted from the dispersed phase into the continuous phase. As the surfactant concentration decreases the interfacial tension increases and hence the droplet size increases in theory (see Equation 1). The number of collisions should reduce as the volume ratio of the phases decreases, the coalescence reduces and the droplet size decreases. In the experiments the volume ratio of the phases decreased from 0.047 to 0.023 during the solvent extraction.

Addition rate of perfluorocarbon phase into the emulsion

The solidification rate was varied by changing the addition rate of the perfluorocarbon into the emulsion. The time needed to add the volume of perfluorocarbon required to extract all the toluene from the dispersed phase (solidification time) varied from 8 to 170 s (Publication IV). The Sauter mean diameter of the microspheres (only spherical particles were

analyzed) increased slightly as the solidification rate decreased. The number of non-spherical particles increased as the solidification rate decreased. One explanation for the formation of non-spherical microspheres at a slow solidification rate was that the solidifying droplets were stretched by the shear forces. The stretched droplets were not restored to the thermodynamically more favorable spherical shape due to the high viscosity of the solidifying droplet. Gasparini et al. (2008) noticed a similar trend: the number of elongated particles increased as the solidification rate decreased. Some microspheres had also collided during the solidification process forming agglomerates (Publication IV).

A narrow microsphere size distribution was produced in all tested conditions and the microsphere size distribution did not change significantly, even though the solidification rate was varied.

Some deposition of the matrix material (= MAO) on the wall of the preparation vessel was noticed especially at the two slowest solidification rates. Not all of the solidifying droplets were properly dispersed in the bulk liquid during microsphere preparation. Hence, some of the solidifying droplets separated and accumulated on the wall forming a solid white deposit.

Samples were taken via needle and syringe from the emulsion during the solidification at different solidification degrees. The samples were injected into 10 ml septa vials to investigate whether solid microspheres had formed. The results indicated that the microspheres had a solid crust when the matrix material (= MAO) concentration in the toluene was approximately 83 wt-% but still contained too much solvent inside the microsphere to stay solid. Jeyanthi et al. (1996) used a similar approach to evaluate the solvent removal and the solidification degree of the microspheres.

Temperature of added perfluorocarbon

The temperature of the continuous phase used to solidify the emulsion droplets did not have a major effect on the size of the microspheres and the microsphere size distribution (Publication V). The mixing conditions were not substantially changed during the solidification, even though the temperature of the emulsion increased as a result of the addition of the hot PFC.

4.2.3 Effect of solidification rate on microsphere morphology

The effect of the solidification rate on the morphology of microspheres was investigated (Publication I). According to theory (see Chapter 2.2;

Figure 2), dense particles are produced if the solidification process is slow enough (especially the solvent mass transfer from the solidifying droplet into the continuous phase). A large difference between the solvent mass transfer rate inside the solidifying droplet and the solvent mass transfer rate from the solidifying droplet into the continuous phase results in the formation of a solid crust, thereby producing hollow microspheres.

Compactness of microspheres

The microspheres were produced using preparation method I (Publication I). The microspheres solidified at low temperature (10°C) were more compact than the microspheres that solidified at higher temperatures (50°C and 90°C; Figure 11). These did not have such a hollow core. The solidification temperature did not have an effect on the diameter ratio of the hollow core to the outer diameter of the microspheres; the ratio was about ~0.44 for microspheres solidified at 50°C and 90°C. The diameter of the hollow microsphere would decrease by only ~3 % if the hollow microsphere formed a compact microsphere (density of microsphere constant). The majority of the toluene is extracted from the droplet before core formation starts. According to the calculation presented in Publication I, core formation starts when the average MAO concentration is ~72 wt-%. This calculated MAO concentration, at which the core is formed, is slightly higher than the value of 67 wt-%, at which deposition of the matrix material on the wall of the preparation vessel was seen (Publication IV). However, the results obtained with preparation method II (Publication IV) indicated that the microspheres have a solid crust when the MAO concentration is ~83 wt-% but still contain too much solvent inside the microsphere to stay solid (see Chapter 4.2.2).

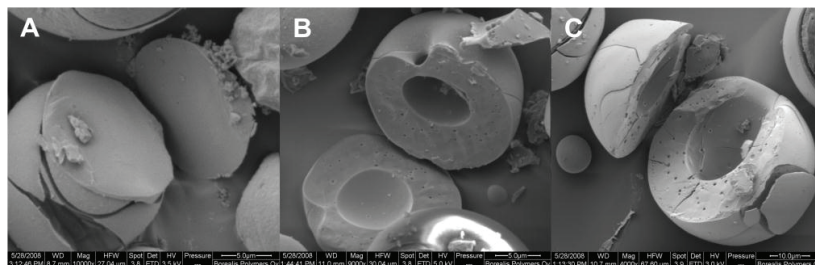


Figure 11. SEM-images from cut microspheres. The microspheres were produced at solidification temperatures of A) 10°C, B) 50°C, and C) 90°C (Publication I).

To obtain dense microspheres the solidification process has to be sufficiently slow (see Chapter 2.2; Figure 2). To slow down the solidification process at 50°C, toluene was added into the perfluorocarbon which was used to extract the toluene from the dispersed phase into the continuous phase (Publication I). The compactness of the microspheres increased with the increasing amount of toluene (Figure 8 in Publication I). All the cut

microspheres (15 particles), which were analyzed with SEM, were compact when 4 ml of toluene was added to the 150 ml of perfluorocarbon used in the solidification. The toluene concentration difference between the phase-equilibrium curve concentration and the bulk concentration of the continuous phase was about the same as in the solidification tests done at 10°C, when 4 ml of toluene was added to the 150 ml of perfluorocarbon (50°C) used in the solidification. The microspheres solidified at 10°C were mainly dense according to light microscopy and SEM images (Figure 11).

The addition of toluene to the perfluorocarbon used in the solidification increased the Sauter mean diameter of the microspheres, although the microspheres were denser than the microspheres prepared without the added toluene. The Sauter mean diameter of the microspheres was 35 and 37 μm , when 2 or 4 ml of toluene was added to the 150 ml of perfluorocarbon used in the solidification step, respectively. The mixing intensity was lower in the solidification step than in the emulsification step, combined with a slow solidification rate, resulted in an increased microsphere size when toluene was added into the perfluorocarbon used in the solidification step. The microsphere size distribution became wider as a result of the toluene addition compared to the experiments done without extra toluene. The microsphere size distribution curves of the experiments, when either 2 ml or 4 ml of toluene was added into the perfluorocarbon, were almost identical.

Porosity of microspheres

The preparation temperature affected the morphology of the microspheres produced using the preparation method II (Publication V). A trend was observed that the matrix porosity of the microspheres increased with increasing preparation temperature. In particular, the microspheres produced at 50°C contained many small holes inside the microspheres (Figures 6 and 7 in Publication V). The solubility of PFC in toluene increases with increasing temperature. Therefore, at higher preparation temperatures more PFC was entrapped in the solidifying MAO droplets forming a greater number of holes in the matrix than at lower preparation temperatures. At higher temperatures, the solidification step was faster than at lower temperatures, which enhanced the entrapping of PFC in the solidifying MAO droplets. A similar trend was seen when the microspheres were produced using preparation method I (Publication I): at a low solidification temperature (10°C) mainly compact microspheres were produced, whereas at higher solidification temperatures (50°C and 90°C) the microspheres produced had small holes inside the microspheres. The holes seen in the microspheres prepared with toluene addition were larger than seen in the microspheres prepared without the toluene addition since

the solidification process (50 °C) was slowed down by adding toluene into the PFC used in solidification. The PFC droplets inside the solidifying droplet had more time to coalesce when the solidification rate was slowed down as a result of the toluene addition. The preparation temperature had no significant effect on the microsphere surface morphology.

5. CONCLUSIONS

Microspheres were produced successfully using a novel emulsion solvent extraction based process. Emulsions normally used in microsphere manufacture processes are oil-in-water or water-in-oil but here a novel hydrocarbon-in-perfluorocarbon emulsion was used. In the first step of the process an emulsion was produced. The dispersed phase of the emulsion contained the matrix material of the microspheres. In the second step of the process, the hydrocarbon from the dispersed phase was extracted into the continuous phase by mixing the emulsion with an excess of the perfluorocarbon. Therefore, the matrix material concentration increased in the dispersed phase as the solvent extraction proceeded. Solid microspheres were formed after all the hydrocarbon had been extracted from the dispersed phase into the continuous phase. The microspheres produced were separated and dried. The variation between the Sauter mean diameter of microsphere batches produced under the same conditions was small in the Publications I-V. The small variation of the replicates indicated that the experiments were repeatable even though the sample for the microsphere size measurement was small and was taken from dry powder. Dry microspheres can segregate by size and therefore taking a representative sample from the dry powder can be difficult.

Experimental results related to this novel emulsion solvent extraction based microsphere preparation process were lacking before this PhD thesis. The critical emulsification and solidification parameters affecting the process are now presented in this PhD thesis. When comparing this process with the normally used oil-in-water or water-in-oil emulsion-based microsphere preparation processes, similar physical phenomena dominated although a hydrocarbon-in-perfluorocarbon emulsion was used.

Microspheres were produced using two different solidification strategies: I) the emulsion formed in a vessel was transferred into another vessel containing an excess of the perfluorocarbon, and II) the excess of perfluorocarbon was added into the emulsion. The tests done using the preparation method I showed that the mixing conditions in both the emulsification and solidification steps affected the size and the size

distribution of the microspheres. The mixing conditions in the solidification step also affected the size of the microspheres, partly because the stability of the hydrocarbon-in-perfluorocarbon emulsion was poor. This was partly due to the high density difference between the hydrocarbon and the perfluorocarbon phase. The mixing conditions during the microsphere production did not change significantly in the preparation method II. Therefore, a narrower microsphere size distribution was produced using the preparation method II compared to the preparation method I.

The size of the microspheres decreased with increasing surfactant concentration, because an increase in the surfactant concentration reduced the interfacial tension between the phases and the coalescence of droplets.

The size of the microspheres decreased with decreasing matrix material concentration. The decrease in the matrix material concentration reduced the viscosity of the dispersed phase. Therefore, the droplets broke up more easily with the decreasing viscosity of the dispersed phase. According to the calculations, the size of the microspheres produced with the preparation method I was mainly affected by the matrix material concentration and not by the changed viscosity of the dispersed phase. However, the size of the microspheres produced with the preparation method II was affected both by the matrix material concentration and viscosity according to the calculations.

The viscosity of the continuous phase used in the emulsification step was varied. The size of the microspheres decreased with increasing continuous phase viscosity because the coalescence of the droplets was reduced.

The size of the microspheres decreased with an increasing Weber number (= with enhanced mixing intensity). The mean size of emulsion droplets and microspheres is known to be a function of the power of the Weber number. The fitted exponent values varied from -0.56 (the preparation method I) to -0.53 (the preparation method II) and were close to the theoretical value, -0.6, which is for a non-coalescing and fully turbulent system. The reasons for the deviation from the theoretical value were that some of the experiments were performed in a transient flow and the studied system was coalescing. An opposite effect was observed at low surfactant concentrations (the preparation method I): the size of the microspheres increased with an increasing Weber number as coalescence increased more than break-up. A surfactant concentration was found at which the size of the microspheres (produced using the preparation method I) remained constant although the emulsification conditions were changed. With preparation method I, the emulsion flow velocity in the solidification vessel and the tip speed of the solidification vessel were combined to obtain a combined emulsion velocity. A good correlation was observed with the

combined emulsion velocity and the size of the microspheres: the higher the combined emulsion velocity, the smaller the size of the microspheres. In the solidification step, the exponent of the Weber number varied from -0.38 to -0.32 (the preparation method I) and therefore was significantly smaller than that observed in the emulsification step. One reason for the deviation between the observed exponent values in the emulsification and the solidification step was the mixing conditions: in the emulsification step the vessel used was baffled whereas in the solidification step the vessel was unbaffled. Therefore, the mixing conditions of the steps differed significantly.

An increase in the volume ratio of the dispersed to the continuous phase led first to a decrease in the size of the microspheres. As the volume ratio of the phases was further increased, the size of the microspheres increased. The size of the microspheres was affected not only by the volume ratio of the phases but also by the surfactant concentration. At a low volume ratio the surfactant concentration was the dominating factor, whereas the volume ratio of the phases was the dominating factor at a high volume ratio of the phases. A correlation between the size of the microspheres (produced using preparation method I) and the volume ratio of the surfactant to the dispersed phase was observed even though the volume ratio of the phases was changed.

The morphology of the microspheres could be controlled by changing the solidification rate, especially the mass transfer of the solvent from the dispersed phase into the continuous phase. The solidification rate was adjusted by changing the temperature of the perfluorocarbon used in the solidification step and the solvent (toluene) concentration in the perfluorocarbon used in the solidification step. The compactness of the microspheres increased with a decreasing solidification rate. Small holes were observed in the matrix material of the microspheres. These small holes were formed because the droplets of the continuous phase were embedded inside the solidifying droplet. The number of small holes in the matrix material of the microspheres increased with a rising preparation temperature, because the solubility of the continuous phase in the dispersed phase increased with increasing temperature.

The number of non-spherical particles increased with a decreasing solvent extraction rate. The solidifying droplets were elongated by the shear forces at the end of the solidification process. The elongated droplets were not restored to the thermodynamically more favorable spherical shape because of the high viscosity of the solidifying droplet. Therefore, non-spherical particles were formed. Some microspheres had also collided during the solidification process forming agglomerates.

The results of this work can be utilized to prepare microspheres using a hydrocarbon-in-perfluorocarbon emulsion solvent extraction based process. However, experiments done in larger scale are proposed to investigate the parameters affecting the emulsion stability. The stability of the hydrocarbon-in-perfluorocarbon emulsion is poor which can make microsphere preparation challenging at larger scale.

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